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ACTION OF ATOPHAN AND NOVATOPHAN IN GOUT AND IRITIS *

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Since the work of Nicolaier and Dohrn[1] showing an increased elimination of uric acid, due to the action of 2-phenylquinolin-4-carboxylic acid (atophan), a great deal of work has been done by many investigators with this substance. All get results showing an increased elimination, but all are not in accord in explaining the mechanism by which this increased elimination is obtained. Weintraud,[2] as well as Frank and Bauch,[3] have concluded from results of experiments in which uric acid was injected and sodium nucleinate was fed, that the atophan acts by increasing the efficiency of the kidney for uric acid elimination. Deutsch,[4] Folin and Lyman[5] and Zuelzer[6] have reached the same conclusion by showing a decrease in the uric acid content of the blood, after the administration of atophan. Retzlaff[7] and Brugsch,[8] as well as Gudzent, Klemperer and Dohrn (cited by Retzlaff), were unable to obtain any decrease in the uric acid of the blood by the action of atophan, but, to the contrary, obtained an increase, which they interpret as indicating a mobilizing action of the atophan.

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* From the Laboratory of Physiological Chemistry, Jefferson Medical College.

1. Nicolaier, A., and Dohrn, M.: Ueber die Wirkung von Chinolincarbonsäure und ihre Derivate auf die Ausscheidung der Harnsäure, Deutsch. Arch. f. inn. Med., 1908, xciii, 331.

2. Weintraud, W.: Zur Wirkung der Stophan bei Gicht, Verhand. d. deutsch. Kong. f. inn. Med., 1911, p. 482.

3. Frank, E., and Bauch, B.: Ueber den Angriffspunkt des Atophans bei seiner Einwirkung auf die Harnsäure Ausscheidung . . . Berl. klin. Wchnschr., 1911, xlviii, 1463.

4. Deutsch. F.: Ueber die Wirkung des Atophans bei Gesunden und Gichtkranken, München. med. Wchnschr., 1911, lviii, 2652.

5. Folin, O., and Lyman, H.: On the Influence of Phenylquinolin Carbonic Acid (Atophan) on the Uric Acid Elimination, Jour. Pharm. and Exper. Ther., 1912-13, iv, 539.

6. Zuelzer, G.: Ueber die Diagnose der Gicht durch Atophan, Berl. klin. Wchnschr., 1911, xlviii, 2101.

7. Retzlaff: Ueber Atophan Therapie bei der Gicht, Deutsch. med. Wchnschr., 1912, xxxviii, 404.

8. Brugsch, T.: Diagnose, Wesen und Behandlung der Gicht, Berl. klin. Wchnschr., 1912, xlix, 1597.

It appears to us, however, that although probably the primary action of the atophan is the stimulation of the kidney, for uric acid elimination, yet it is logical to think of at least an indirect mobilizing action. In normal cases and in non-gouty cases the uric acid elimination, under the influence of atophan, is rather large the first day, and falls after a day or two to a point below normal. This is apparently due to the depletion of the supply of uric acid in the blood, and as there are no deposited urates, there is no replenishment of the depleted blood. In the case of gout, however, there are deposits, which may be mobilized, tending to maintain the blood concentration, thus accounting for the rather high and long-continued increased excretion of uric acid in gout cases, as mentioned by Zuelzer.[6] That the mobilization is not extensive is apparently indicated by the fact that the uric acid content of the blood is lower at the end of the atophan treatment. It seems reasonable to think that as the supply of uric acid in the blood is decreased through the action of atophan, there would be a tendency for the solution of the deposits.

In connection with the mobilizing of deposited urates, the work of Daniels,[9] showing an apparent increase in the uric acid output in gout over that due to atophan, by the use of lithium along with atophan, is of interest. Abl† has suggested the use of other drugs with atophan.

Our studies were conducted on patients in the Jefferson Hospital, and in all instances the subjects were placed on purin-free diets. No attempt has been made to give complete clinical findings.

OBSERVATIONS 1 AND 2.—*Gout.*—N. W., aged 20. (Tables 1 and 2). The patient had a marked hypertrophy of the left ventricle, had had several severe dilatations, chronic interstitial nephritis, numerous tophi in the ears, and arteriosclerosis. Blood-pressure was high as a result of the arteriosclerosis.

TABLE 1.—OBSERVATION 1, GOUT

	Urine		Blood (100 gm.)	
Day	Vol. c.c.	Uric Acid gm.	Uric Acid mg.	Atophan gm.
1	1,975	0.217		
2	1,625	0.068		
3	2,474	0.087		
4	2,282	0.084		
5	2,064	0.101	2.54	3
6	2,077	0.101	....	3
7	1,805	0.054	1.60 *	3
8	1,216	0.097		
9	1,898	0.127		
10	2,530	0.157		
11	2,438	0.144		
12	2,590	0.121	1.71	

* Taken at the end of Day 7.

9. Daniels, Amy L.: The Influence of Lithium and Atophan on the Uric Acid Excretion of a Gouty Patient, THE ARCHIVES INT. MED., 1914, xiii, 480.

† Abl: Arch. f. exper. Path. u. Pharmakol., 1914, lxxiv, 119.

TABLE 2.—Observation 2, Same Case as in Table 1

Day	Urine Vol. c.c.	Urine Uric Acid gm.	Blood (100 gm.) Uric Acid mg.	Atophan gm.
1	2,182	0.205		
2	1,780	0.161		
3	1,712	0.221	4.88	5
4	1,622	0.208	....	5
5	1,915	0.216	3.44 *	5
6	1,370	0.147		
7	2,280	0.207		

* Taken at the end of Day 5.

There were no active symptoms of gout during the first observation, but on the morning of the final day, the patient complained of slight soreness in both great toes. The diet was supposedly continued purin-free between the two periods, but the patient received chicken at least once during that time; the exact day he received it, is, however, uncertain.

At the beginning of the second observation, both toes were swollen, inflamed and very painful. At the end of the second day of atophan treatment, the symptoms were much improved. The toes were still swollen, and at the end of the third day were about the same. After the atophan was stopped the symptoms reappeared, although not to the same extent. There was no noticeable change in the tophi, under the atophan treatment, as reported by Richter.[10]

In the "very severe case of gout" cited by Folin and Lyman,[5] the atophan caused neither an increased uric acid elimination nor a diminished uric acid value of the blood, the blood containing the normal amount of uric acid. In our case, although the content of uric acid in the blood was normal, we obtained an appreciable reduction, although the increase in elimination was exceedingly slight. The case is of considerable interest because of the exceptionally low uric acid elimination.

In the case reported by Folin and Lyman, the rise in the uric acid content of the blood seems to be due to the decreased elimination. The increase noted in our case is apparently not to be accounted for in the same manner, as there was an accompanying increase in elimination.

Observation 3.—*Iritis.*—M. P., laborer, aged 55. Ulcerative keratitis. Patient was attending a brush fire and the wind blew some sparks and smoke into his eye. Previous treatment, atropin after sweats. Sweats discontinued with the start of this experiment. Discharged, much improved.

10. Richter, Paul Friedrich: Ueber Wesen und Behandlungen der Gicht, Deutsch. med. Wchnschr., 1911, xxxvii, 2361.

TABLE 3.—Observation 3, Iritis

Day	Urine Vol. c.c.	Urine Uric Acid gm.	Blood (100 gm.) Uric Acid mg.	Atophan gm.
3	1,000	0.263		
4	1,000	0.274		
5	1,000	0.274		
6	(Lost)			
7	1,210	0.293		
8	1,090	0.274		
9	1,000	0.270	1.4	5
10	1,000	0.307	...	5
11	1,090	0.273	0.4 *	5
12	458	0.253		
13	965	0.366		
14	1,000	0.146		

* Taken at the end of Day 11.

In the table, all urines recorded as 1,000 c.c. volume were very concentrated, and contained sedimented uric acid and urates. These were dissolved in sodium hydroxid and then the whole amount made up to 1 liter with distilled water. The volumes averaged about 300 or 400 c.c.

The iritis seemed to clear up rapidly under the influence of the atophan, although the uric acid elimination was not influenced.

Observation 4.—*Iritis.*—C. S. aged 35. Had two children, no miscarriages. No venereal infection. Never any acute articular rheumatism. Family history negative. Patient would not remain for the completion of the experiment, and would not permit of the taking of a final blood sample, for no apparent reason, except possibly because of menstruation, which occurred during the course of the experiment.

TABLE 4.—Observation 4, Iritis

Day	Urine Vol. c.c.	Urine Uric Acid gm.	Blood (100 gm.) Uric Acid mg.	Atophan gm.
1	1,500	0.297		
2	1,310	0.312		
3	800 *	0.206		
4	760 *	0.135		
5	1,450	0.278		
6	2,010	0.348		
7	1,295	0.317	0.66	5
8	1,005	0.225	....	5
9	1,065	0.169	....	5

* Probably some of these two samples were lost, although the nurses claimed the samples were complete.

In both cases of iritis (Observations 3 and 4), there was no appreciable increase in the uric acid elimination due to the atophan, although in the first case there appeared to be a slight delayed increase, similar to one recorded by Deutsch.[4] Haskins[11] also noted a delay in the time

11. Haskins, H. D.: The Effect of Atophan and Novatophan on the Endogenous Uric Acid Excretion of Normal Men, Jour. Pharm. and Exper. Ther., 1913, v, 63.

of appearance of the uric acid increase. The explanation for the lack of increase in uric acid excretion in iritis, as well as for the clearing up of the trouble under the atophan, in both our cases, is not apparent. It may be that atophan has an important action totally unrelated to uric acid. May this not be due to the antiphlogistic action of atophan which Starkenstein and Wiechowski[12] have demonstrated? We hope to investigate this point.

Observation 5.—*Acute Rheumatic Fever and Pericarditis.*—G. R., aged 18. All joints limited in motion. Distinct pain over vertebrae. Right wrist and hip most sensitive. Widal positive. Wassermann negative. Data in regard to history, both personal and family, very indefinite, although there was apparently no family history of gout. Had been receiving ferrosalicylate, and had also received, some time after the salicylate was stopped, 5 gm. of atophan per day for a period of five days. This was stopped the morning our observation period began. He had also received sodium bicarbonate, aspirin, and an occasional hypodermic injection of morphin to relieve pain. The sodium bicarbonate was continued throughout the observation period.

TABLE 5.—Observation 5, Acute Rheumatic Fever and Pericarditis

Day	Urine		Atophan
	Vol. c.c.	Uric Acid gm.	gm.
1	855	0.214	
2	710	0.212	
3	2,385 *	0.501	
4	920 †	0.313	
5	2,025	0.579	5
6	1,370	0.343	5
7	1,590	0.398	5
8	2,005	0.479	5
9	1,800	0.432	5
10	2,230	0.540	5
11	1,515	0.324	
12	2,610	0.596	
13	1,315	0.250	
14	1,825	0.593	
15	1,370	0.607	

* Patient (without our knowledge) was given two cups of water every half hour during the day, which may explain the large increase in uric acid eliminated, although little is known as to the effect of water ingestion on the uric acid output.

† Patient perspired excessively throughout the day and night.

After the atophan was stopped, previous to the observation period, the patient became worse, the pain increasing, and on Day 3 of the experimental period, patient had a temperature of 102.5. On the administration of atophan, the pain disappeared, and the patient was able to sit up in bed, feeling much improved. There was not a second relapse similar to the first during the time the patient continued under our observation.

12. Starkenstein, E., and Wiechowski, W.: Ueber die Pharmakologie des Atrophaus, Prager med. Wchnschr., 1913.

According to Zuelzer,[6] who finds in all cases of gout a rather marked increase in uric acid output, continued over a long period of time, and in all non-gouty joint affections, a smaller increase over only one or two days, this case would be considered as of a gouty nature. A similar rather high and uniform increased elimination is to be noted in the case of J. S. B., Observation 6, which case was diagnosed as gouty.

The increases of Days 12, 14 and 15 are rather peculiar, and not easily accounted for, unless as a delayed increase from the long atophan period.

OBSERVATION 6.—*Arteriosclerosis and Gout.*—J. S. B., bar-tender, aged 55. Rheumatic pains about shoulders and upper back. Alcoholic. No family history of gout or similar conditions. No previous history of rheumatism or lues.

TABLE 6.—OBSERVATION 6, ARTERIOSCLEROSIS AND GOUT

	Urine		
Day	Vol.	Uric Acid	Novatophan
	c.c.	gm.	gm.
1	1,380	0.426	
2	2,565	0.416	
3	1,970	0.384	
4	2,095	0.543	5
5	2,250	0.563	5
6	1,980	0.521	5
7	2,040	0.314	
9	2,245	0.294	
9	1,870	0.391	
10	1,790	0.403	

In this case results, similar to the usual results with atophan, were obtained with novatophan. The patient felt very much better while receiving the novatophan, and the discomfort in the shoulders returned, although not to the same extent, after the treatment was stopped. It is probable that the elimination would not have remained so uniform (see Days 4, 5 and 6) had the administration of the novatophan been continued for a longer period.

In one case in which atophan was given in tablet form, no difficulty was experienced in regard to an unpleasant taste. In the other cases gelatin capsules were used. In no case were there any untoward symptoms, as for example the scarlatiniform rash, noted by Herrick.[13]

Skorczewski and Sohn[14] report that atophan urines respond in the characteristic manner to Ehrlich's diazo reaction. They are substantiated by Dohrn.[15] We were unable to obtain the typical reaction in any

13. Herrick, W. W.: A Scarlatiniform Rash from Atophan, Jour. Am. Med. Assn., 1913, lxi, 1376.

14. Skorczewski, W., and Sohn, I.: Ueber einige in Atophanharne auftretende characteristische Reaktionen, Wien. klin. Wchnschr., 1911, xxiv, 1700.

15. Dohrn, Max: Ueber Farbreaktion speziell die Diazoreaktion im Atophanharn, München. med. Wchnschr., 1912, lix, 568.

case. A similar reaction was obtained, but easily differentiated from the characteristic one.

Owing to previous difficulties experienced in the collection of blood samples, the uric acid was not determined in the blood during Observations 5 and 6. In determining the uric acid in blood, we followed slight modifications of the method of Folin and Denis[16] as suggested by Myers and Fine.[17] The oxalated blood was poured into about four volumes of boiling distilled water, with stirring, and again brought to a boil. Hundredth-normal acetic acid was then added to complete coagulation, about an equal amount being required. The procedure from this point on was the same as the original. In all cases (both blood and urine) three drops of concentrated hydrochloric acid, instead of one drop as called for by the method of Folin and Denis[18] were added along with the hydrogen sulphid used to decompose the silver urate.

We wish to express our indebtedness to Drs. McCrae, Solis-Cohen, Hansell and Sweet of Jefferson Hospital for permission to study the cases herewith reported. We are also indebted to Drs. Burns, Clerf, Dry, Livengood, Lummis, Shannon, and Wayland, as well as the nurse in attendance, for care and assistance in the collection of blood samples and the handling of the cases.

16. Folin, O., and Denis, W.: A New (Colorimetric) Method for the Determination of Uric Acid in Blood, Jour. Biol. Chem., 1913, xiii, 469.
17. Personal communication.
18. Folin, O., and Denis, W.: Jour. Biol. Chem., 1913, xiv, 95.

THE RADIO-ACTIVITY OF THE MINERAL WATERS OF HOT SPRINGS, WARM SPRINGS AND HEALING SPRINGS IN HOT SPRINGS, VA.*

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The study of radium and radio-activity long ago became a subject of great interest, not only for the pure scientist, but also for the physician and his patients. The search for radium-containing ores in this country, while it has been successful in demonstrating the wealth contained in the earth, has also evidenced the great scarcity of this metal. It is important, therefore, to study the numerous springs of this country in the light of their radio-activity. Although the analyses made in this country are not numerous, it is to be hoped that in the course of years the contributions to our knowledge of the radio-active properties of our springs will become more numerous. It is with this aim that the following investigations were undertaken. Before detailing the results of these investigations, a few historical facts may be pertinent.

Since the discovery of the "x-rays" by Roentgen[1] in 1895, numerous scientific facts have been revealed; for example, the Becquerel or the "canal" rays of Goldstein (1898), the radio-active properties of uranium, the isolation of polonium and radium (Schmidt and Madame Curie,[2,3] Giesel,[4] Marckwald[5]), of thorium (Hahn[6]), of actinium (Debierne,[7] 1899), the ekalathan (by Giesel[8]) and the radiothor (by Marckwald in 1902). The study of the chemical and physical properties of these substances and of the products resulting from their continuous disintegration, led to the discovery of different rays (alpha, beta, gamma), to whose action the chemical-biological effects of radio-active substances must be attributed.

* Submitted for publication May 5, 1914.

1. Cited according to Rutherford: Radioactive Substances and Their Relations, 1913, p. 6.
2. Curie, P. and S.: Compt. Rend. de l'Acad. d. Sc., 1898, cxxvii, 1215. Curie M. and Mme., and Bemont, G.: Compt. Rend. d. l'Acad. d. Sci., 1898, cxxvii, 1215.
3. Hampson: Radium Explained, p. 20.
4. Giesel: Ann. d. Physik., 1890, lxix, 91; Ber. d. deutsch. Chem. Gesellsch., 1902, p. 3608.
5. Marckwald: Physikal. Ztschr., 1903, iv, 51. Ber. d. deutsch. Chem. Gesellsch., 1903, p. 2262.
6. Hahn: Proc. Roy. Soc., 1905, lxxvi, 115; Phys. Ztschr., 1907, viii, 277; ibid., 1908, ix, 392.
7. Debierne: Compt. Rend. de l'Acad. d. Sc., 1899, cxxix, 593; ibid., 1900, cxxx, 206.
8. Giesel: Ber. d. deutsch. Chem. Gesellsch., 1902, p. 3608; ibid., 1903, p. 342.

Besides these different rays, emanation was discovered as a constant decomposition product in connection with radium and thorium, as well as in actinium (1900 Dan). The emanation, a gas of an evanescent character, diffuses rapidly into the surrounding air and is readily dissolved in water, and in contact with other substances the radio-active properties of this emanation are imparted to the former, so creating excited (induced) radio-activity. Emanation that contains alpha rays is radio-active and as such ionizes the air. As a gas it is subject to the laws of diffusion and is condensed at a temperature of minus 185 C. Its qualities can be preserved in a latent stage (Ebert,[9] Rutherford and Soddy[10]). The atomic weight of emanation, according to Ramsay[11] and Sommer,[12] is 218.5; its half-time or half-value (that is, in that time the substance will have lost 50 per cent. of its original strength of radiation) is 3.8 days. Dry emanation under considerable heat rapidly splits up and produces helium. Moist or dissolved in water, the decomposition product is called neon (atomic weight 20). In the presence of copper salts argon (atomic weight 40) is formed. Elster and Geitel[13] were the first to detect the frequency of emanation as present in the air, in the soil, in caves, in the atmospheric precipitations (rain, snow). In England, G. Thompson[14] in Cambridge, in Italy, Pocchettino and Sella in Rome,[12] demonstrated radio-activity and radio-emanation in the air and in the waters. Since 1903 these facts have been confirmed by numerous investigators (Thompson, Allen, Himstedt,[15] Lord Blytheswood, Strutt, Elster and Geitel,[13] Dom, Schenck, Mache). A review of the literature on radio-activity of mineral waters, and of the by-products and sediments found in spas, would certainly be of interest, but would surpass the aims of the present paper. It seems, however, that the most numerous contributions in this line have been carried out by German and Austrian investigators, so that the most renowned spas can be compared with regard to their radio-activity (Joachimstal, Brambach, Gastein, Lacco Ameno (Ischia), Carlsbad, Baden-Baden, Baden b. Wien, Teplitz, Nauheim, Marienbad, Franzensbad Dürckheim, Kreuznach, Muenster, Landeck in Silesia and others).

9. Ebert: Ber. d. Bayr. Acad. d. Wissensch. München., 1903, xxxiii, 1333.
10. Soddy: The Interpretation of Radium, 1912.
11. Ramsay: Jour. London Chem. Soc., 1907, xci.
12. Sommer, in Emanation and Emanationstherapie (Gmelin), 1909.
13. Elster and Geitel: Phys. Ztschr., 1900, i, 11; ibid., 1901, ii, 116, 560, 590; cited by Rutherford (Footnote 1, p. 340); Engler and Sieveking: Radium in Biol. u. Heilk., 1912, i, 277.
14. Cited according to Rutherford (Footnote 1, p. 641).
15. Himstedt: Ann. d. Phys., 1903, xii, 107; ibid., 1904, xiii, 573; cited by Engler and Sieveking (Footnote 13, p. 270).

METHODS OF THE DETERMINATION OF RADIO-ACTIVITY

For the determination of radio-activity of fluids, gases, sediments and stones, different methods have been recommended, such as:

(*a*) The test on the fluorescent screen as compared with standard radium preparations.

(*b*) The action on the sensitized photographic plate, as compared with standard radio-active compounds.

(*c*) The measurement of the ionized air, produced by the emanation contained in radio-active fluids, solids and gases.

The latter method is the one most frequently used and gives good results. This can be done as follows:

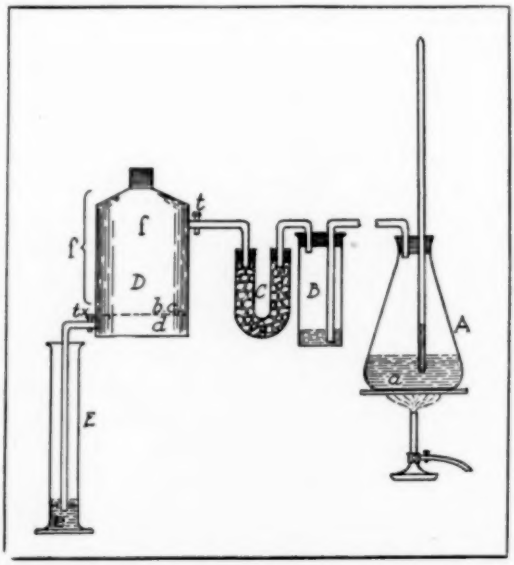

Fig. 1.—Diagram of apparatus for testing the radio-activity of dissolved and gaseous emanation in spring waters: A, flask; B, wash-bottle; C, absorption tube; D, Gas tank; E, measuring-glass; t, tx, taps; a, mineral water; b, normal loss for ordinary tap water; d, radio-activity of remaining tank water after passage of gas; e, radio-activity of escaped water from tank; f, radio-activity of gas mixture in tank.

1. By circulating the emanation through the electroscope. By pressure the emanation is liberated from the water and then reaches the electroscope by a closed system. In this apparatus the charged leaflets of the electroscope lose their electric charge more or less rapidly, according to the ionization of the air containing the emanation. By means of a microscope the rapidity and the distance of the leaflets is read off from a scale. Such a method was first recommended by

Elster and Geitel[16] and has been used since by different investigators — Boltwood,[17] Schlundt and Moore,[18] and others. Different causes of error have to be eliminated; for example, the rubber connections and the glass tubing can absorb the emanation, or the mechanical propulsion may be at fault and thus an irregular circulation of the emanation may result. Instead of forcing air through the fluid, which drives off the emanation, the radio-active water can be boiled. In this manner the emanation escapes rapidly and can be measured in the electroscope. This method gives some higher values than the one previously mentioned. If sediments or minerals are to be examined, these are either dried or calcinated and the emanation that escapes can be collected and measured.

2. Engler and Sieveking[19] adopted another manner of procedure which is as follows: The water, under the necessary precautions, is poured into a given tank, and after hermetic closure by a well-fitting rubber stopper, is shaken vigorously for one-half to one minute. If the mineral water should contain a considerable amount of free carbonic acid, this chemical substance, freed from the water, increases the pressure in the tank. Occasionally the rubber stopper may be blown off and with it a considerable loss of emanation may result. To avoid such an accident a small amount of water is allowed to escape through a small tap at the bottom of the tank, without any gas, in order to restore the normal pressure. By shaking the water the emanation is driven into the air, and only about 2 per cent. of the original amount remains dissolved in the fluid. The fontactoscope from Engler and Sieveking is the apparatus most frequently used in the tests reported in the literature, for comparative measurements with this method gave results as close to those control tests as could be obtained by any other laboratory method. In our investigations we also used the fontactoscope of Engler and Sieveking, the dispersion factor of the apparatus being indicated as 13.8. The technic which we followed was, in brief, as follows:

1. Determination of the electric conductivity of the tank containing ordinary air, ascertained by successive reading of the distance of both leaflets of the electroscope during one hour. Each fraction of the scale corresponds to a certain electric tension in volts, and so the normal loss for each determination was ascertained. According to the time of the day, the weather, the humidity of the surrounding air, this normal loss differed from the previous determinations. In cases in which the figures obtained were high, owing to the accumulation of humidity in the apparatus, the air was dehydrated by the introduction of a small amount of metallic sodium left in the capsule of the electroscope. After this the normal loss became smaller.

16. Elster and Geitel: Phys. Ztschr., 1905, v, 32.
17. Boltwood: Am. Jour. Sc., 1904, Series 4, xviii, 97; 1905, xx, 128.
18. Schlundt and Moore: U. S. Geol. Survey, 1909, Bull. 315.
19. Engler and Sieveking: Radium in Biol. u. Heilk., 1912, i, 277.

2. Determination of the radioactivity of the normal mineral water. After a qualitative test had demonstrated the presence of radio-activity in the water, a measured quantity of the water was collected from the spring under the proper precautions in a hermetically closed glass container, transferred as quickly as possible to the laboratory; immediately placed in the gas tank, shaken for one-half to one minute, the electroscope rapidly adapted, charged with positive electricity and the first reading of the distance of the leaflets taken. A stop-watch marked the fractions of minutes, and at regular intervals, as recorded on the tables, the distance of the leaflets was ascertained. In most instances the highest readings were obtained in one-half minute from the beginning of the experiment. The readings were continued up to an hour or even longer. These figures, representing the distance of the leaflets, correspond to so many volts as indicated in the table, and warranted by the manufacturer of the instrument. After deduction of the normal loss of tension as found for air, these figures then were computed for one liter and for one hour's time, and the volt-hour pro liter mineral water was found. In most of the results published by other investigators we find the radio-activity rendered in electrostatic units,

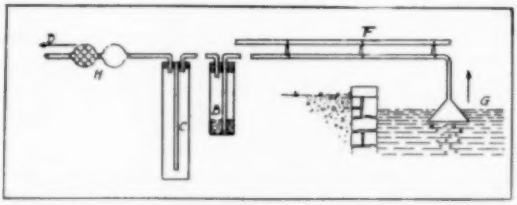

Fig. 2.—Method of collecting the escaping gas from the spring for the examination of radio-activity: F, stick supporting funnel, G, which is connected with the wash-bottle, B, the dehydrating tube, C, and the aspiration bulb, H.

or, as these figures usually are exceedingly small, this product multiplied by 1,000 is quoted as Mache units (M.-U.). In our tables the values correspond to Mache units per liter water and per hour. For our purposes no corrections, as for the induced radio-activity formed in the gas tank, or the residual activity as contained in the remaining water, were made. Such corrections amount to a few Mache units only in the average cases and they would not change materially the results obtained. In each determination of the radio-activity of mineral water a normal test preceded, and that was made after careful washing of the gas tank with ordinary tap water so that any remaining induced activity could be excluded. For therapeutic purposes a small difference in Mache units can hardly be of great importance.

In the progress of our investigation we were impressed by the observation that even in taking the greatest precautions a loss of emanation could not be prevented; even then when we did not lose any time before the determinations were begun. This observation was strengthened by the marked difference in the results of the determination of Healing Springs and of Warm Springs. In both instances the samples determined in the laboratory and the readings taken immediately at the spring itself, demonstrated the superiority of the field determinations (differences from 84.7 to 90.8 per cent.), provided favorable meteorological conditions prevailed. Several field tests at the source were carried out and accordingly more accurate readings were

obtained. After each determination of mineral water the tank was carefully washed out with ordinary tap water in order to remove the induced radio-activity adhering to the walls of the gas tank. In some of the tests the mineral water was left for a given time in an open or closed jar and then the radio-activity ascertained. In some instances in the closed jar the emanation collected still showed high values. Further observation, however, revealed, by the quick loss, that most of the ionization of the air was due to emanation gas and not to radio-active substance in solution.

In some springs the amount of dissolved emanation was ascertained by boiling a given amount of mineral water. The following description may help to an understanding of the procedure:

Flask A (Fig. 1) is provided with a long glass tube ending in a fine capillary point (to avoid over-pressure by the escape of air), the lower end reaching to the bottom of the flask. Connected with the boiling flask is the wash-bottle B, to retain any impurities that might be driven over from A. In connection with B is the absorption tube, C, filled with calcinated calcium oxid, for the absorption of humidity and vapors. Glass and rubber tubing connect C with the gas tank D, provided with several taps, t, and tx, and a well fitting rubber stopper at the top. Connected with the gas tank through the tap, tx, is the measuring glass, E, to receive the escaping water from the gas tank.

Previous to the testing of the dissolved radio-activity of the mineral water the following determinations are necessary: (1) Conductivity of the gas tank filled with air. (2) Conductivity of the ordinary tap water with which the tank is to be filled to the brim. After these values have been obtained, a given amount of mineral water (a) is boiled for five minutes in the flask A, then the tap, t, is opened and also tx; slowly the water is emptied from the gas tank, D, and measured in the receiving vessel, E, and a certain amount of it, e, tested for its radio-activity. A slow suction is maintained by the outflowing water and this is continued until eight liters of water escape, leaving only about two liters of water in the tank D (the radio-activity of which is also later ascertained (d); the remaining quantity (f) constitutes the air and emanation aspirated from the system of containers (A, B, C). The determination of the radio-activity of the air and fluid in tank D is not started until the taps t and tx are closed and after the gas tank has cooled down to room temperature.

For the computation of the result all these findings are taken into consideration. For example, the degree of radio-activity is ascertained as follows: (1) radio-activity of the collected gas in tank $D = f - b$ (normal loss of air); (2) radio-activity of remaining tank water $= d - b$ (normal loss of air); (3) compared with radio-activity of the same amount of ordinary tank water $= c - b$; (4) radio-activity of the outflowed water in the receiving tube, E, $= e - b$ (normal loss of air). The total value of the computation consisted of $1 + (2-3) + 4 = (f-b) + [(d-b) - (c-b)] + (e-b)$ the value of which was found higher than if only $D = (f-b)$ was considered.

As seen from the different tables from different springs a given amount of mineral water was evaporated to dryness and then the salt residue tested for its radio-activity. In almost all instances a low conductivity could be ascertained, from which fact one may conclude that in the springs most of the radio-activity must result from the dissolved emanation gas.

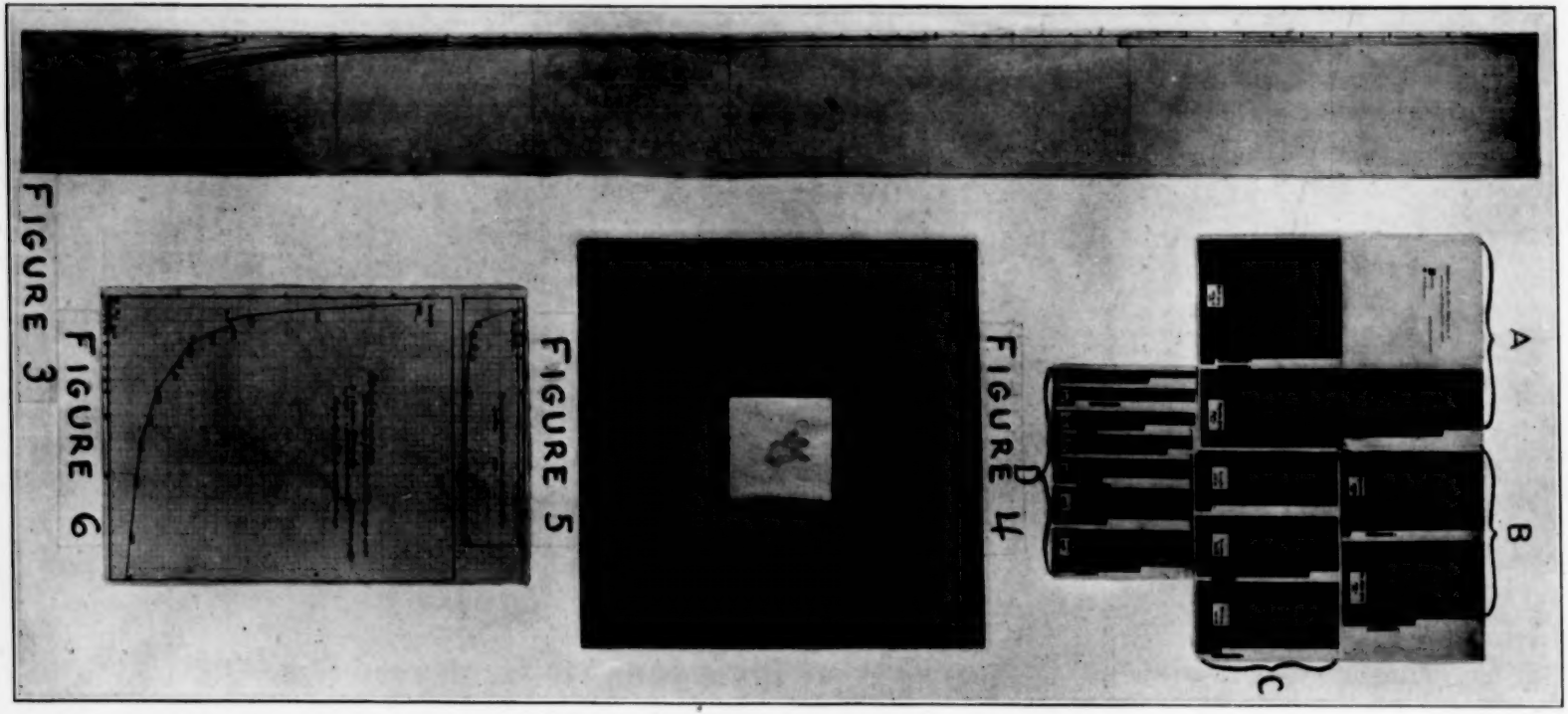

Fig. 3.—Chart representing a comparison of the radio-activity of the different springs at Hot Springs, Warm Springs and Healing Springs at Hot Springs, Va., per liter and per hour in Mache units.

Fig. 4.—Graphic representation of the radio-activity of springs at Hot Springs, Va., in Mache units in a full bath of 200 liters (50 gal.): A (from left to right), Boiler Spring, 48,219.66 M. U.; Magnesia Spring, 56,918.3 M. U.; B, Open Well, 31,326.84 M. U.; Hot Sulphur Spring, 31,562.2; C, Swimming Pool, 21,855 M. U.; Thermal Water, August Spring, 22,503.3 M. U.; Warm Springs, 26,800.5 M. U.; D (from left to right), Spout Spring, 4,207.2 M. U.; Octagon Spring, 5,136.6 M. U.; Cold Spring (north), 6,338 M. U.; Club House Spring, 6,631.9 M. U.; 102 T. Spring, 8,017.2 M. U.; Soda Spring, 12,906.7 M. U.

Fig. 5.—Represents the difference between the radio-activity of the swimming-pool at Warm Springs (white field in center) and the swimming-pool at Hot Spring (black square). The squares are drawn to a scale of 100 Mache units.

Fig. 6.—Chart showing in the upper curve the radio-activity of the dry substance of 1,000 c.c. of Boiler Spring water. The lower diagram refers to the radio-active gas escape of the same spring measured alone and indicated by the heavy columns at the bottom of the chart, and the dissolved emanation found in the tank water, represented by the curve above.

A few tests were also carried out to determine the radio-activity of the gases escaping directly from the springs. For a better comprehension of the method adopted the following description may be useful:

The arrangement of the apparatus (Fig. 2) does not differ much from that previously described. Instead of the boiling flask a rubber and glass tube, suspended on a long stick, F, has as its opening a funnel, G, which is held in direct contact with the water surface, exactly over a spot where the gas bubbles arise from the bottom of the spring. Between the gas tank, D, and the dehydration tube, C, if necessary a rubber aspiration bulb, H, is inserted through

TABLE 1.—Comparison with Some European Spas of the Different Springs Examined at Hot Springs, Healing and Warm Springs, Va., as to Their Radio-Activity, and Their Strength per One Full Bath (50 Gallons 200 Liters)

Spring	Temp. F.	Water	Gas	Dry Residue	Total	Dissolved Emanation	Per Full Bath—M. U.	Compares with
1	102	16.551	2.012	2.474	21.037	54.676	4,207.256	Neundorf a. Soden.
2	99.0	4.889	12.832	7.962	25.683	3.399	5,136.642	Muenster Nauheim.
3	52.5	31.691	.....	.....	.....	.....	6,348.32	Nauheim.
4	102.5	33.16	.....	.....	.....	.....	6,631.972	Higher than Nauheim.
5	102.0	15.709	21.128	3.160	40.086	18.002	8,017.292	Higher than Nauheim.
6	75.0	64.534	?	?	?	.....	12,906.756	Higher than Kreuznach; less than Baden-Baden.
7	84.0	69.621	13.335	3.513	86.47	80.419	16,083.788	Between Kreuznach and Baden-Baden.
8	63.25	92.63	?	?	?	?	18,526.252	
9	81.5	109.273	.....	.....	.....	.....	21,855.467	
10	73.0	112.517	.....	.....	.....	.....	22,503.384	Little less than Baden-Baden.
11	96.3	95.72	32.41	5.87	134.002	.....	26,800.502	Higher than Baden-Baden.
12	90.25	156.63	.....	.....	.....	.....	31,326.836	Higher than Gastein.
13	99.4	101.87	54.94	1.22	157.811	75.60	31,562.228	Higher than Gastein.
14	104.0	86.54	152.18	2.38	241.198	66.234	48,219.669	Higher than Gastein and Landeck.
15	98.2	260.95	21.52	2.14	284.592	61.06	56,918.2	Higher than Landeck.

The highest radio-activity in swimming-pools (so far as our knowledge goes) is found in the Warm Springs swimming-pool, exceeding the values found in the Radium Kurhaus at Joachimsthal and represented by the figures found at Brambach (Voigtland).

Name of Springs examined: No. 1. Spout Spring; 2. Octagon Spring; 3. North Cold Spring; 4. Clubhouse Casino Spring; 5,103° T. Spring; 6. Soda Spring; 7. Healing Springs; 8. South Cold Spring; 9. Swimming Pool at Hot Springs; 10. August Spring (Thermal Water); 11. Warm Springs; 12. Pipe Spring (open well); 13. Hot Sulphur Spring; 14. Boiler Spring (used in bath-house); 15. Magnesia Spring. The numbers of the different springs correspond to those indicated in the tables.

which, by gentle pressure, the gas escaping far below the surface of the spring may be aspirated. The arrangement of the wash-bottle, B, the gas tank, D, and the recipient, E, is just the same as in Figure 1 and the entire technic is carried out as already described. In making the tests about 8 liters of water were withdrawn from the gas tank, D, taps t and tx were closed and the entire apparatus was then hurried to the laboratory, where the different determinations followed immediately. (See preceding determination of gas emanation). At Healing Spring and at Warm Spring the gas tests were made immediately at the spring. Also was the air in the bath cells of Hot Springs collected in a similar way, after securing a hermetic closure of all the outlets of the bath cell. The necessary corrections (as mentioned) were considered in the computation of the final results.

COMPUTATION OF THE READINGS

As already mentioned, the tension in volts calculated from the readings can be tabulated in a variety of ways. For mineral waters the Mache unit for one liter of water for one hour has been adopted, or the electrostatic unit (1/1,000 Mache units). Another method would be the comparison with the emanation resulting from the saturation current of 1 gram of radium ($5,3 \times 10^{-5}$ electrostatic units), corresponding

TABLE 2.—TESTS OF RADIO-ACTIVITY MADE ON BOILER SPRING WATER. TEMPERATURE 104 F.

Time Min.	1		2		3		4		5	
	Volts	M. U.	Volts	M. U.	Volts	M. U.	Volts	M. U.	Volts	M. U.
½	4,779.4	60.70	951.6	12.09	939	11.93	11,982.5	152.18	6,862.5	87.15
1	5,239.86	54	711.6	9.04	759	9.24	9,899.9	125.73	4,638.0	58.90
1½	3,699.4	46.98	671.0	8.53	...	.....	9,568.0	86.55	3,190.5	40.63
2	3,299.4	38.14	611.6	7.78	468	5.94	6,588.6	83.29	2,670.7	33.92
2½	3,003.4	38.14	.....	.....	...	.....	6,306.52	80.09	2,670.7	33.92
3	2,739.4	34.79	511.6	6.50	499	6.35	5,687.92	72.24	2,345.0	29.78
4	1,289.4	16.38	381.6	4.85	444	5.64	4,928.14	61.59	1,819.8	23.17
5	1,971.4	25.04	302.6	3.84	399	5.07	7,925.36	1,000.78	1,651.2	20.97
6	1,639.4	20.82	291.6	3.7	...	.....	4,087.82	51.81	1,457.75	18.51
8	112.15	1.42	254.1	3.08	...	.....	3,608.84	45.83	1,073.6	13.63
10	101.8	1.29	225.6	2.87	213	2.71	3,389.38	43.05	898.05	11.41
12	91.9	1.17	186.6	2.37	...	.....	3,162.92	40.27	717.5	9.11
15	69.8	0.89	183.6	2.33	155	1.97	3,005.2	38.17	596.0	7.57
21	53.63	0.68	.....	.....	123	1.56	3,073.06	38.26	457.05	5.80
30	67.0	0.47	123.6	1.57	...	.....	2,673.16	33.85	359.6	4.56
60	.....	.....	122.6	1.57	...	.....	.....	.....	.....	....

EXPLANATION TO TABLE 2

1. Test carried out at the spring, avoiding transport of the water; values given in volts and Mache units per hour and test 1,000 c.c. net, after deduction of the normal loss for air in the tank.
2. Same water taken under all precautions but determination made upstairs in the radiological laboratory of the bath-house (loss of time necessarily involved four to five minutes).
3. Boiler Spring water allowed to stand for twenty-two hours in closed jar; notice the remarkable difference in the determination compared with 1 and 2.
4. Gas radio-activity escaping from Boiler Spring, collected under precautions described in text; 2,500 c.c. in twelve minutes; values given for radio-activity of tank water and tank air combined, as the tank water readily absorbs the radio-emanation; more than 90 per cent. (97 to 98 per cent.) is found in the water, whilst the air mixture contains a small percentage of radio-emanation (see Fig. 6).
5. Boiler Spring allowed to flow in bath-tub during twelve minutes and twenty-four seconds; then sample of air collected from the bath-cell, all windows, doors and possible outlets being kept closed during that time. Aspiration of air begun 2 minutes after start of experiment; 2,000 c.c. of water subtracted from water tank during aspiration of about 5,450 c.c. of air.
Emanation total from tank air, in residual and escaping tank water.

to 0.57 c.c. of emanation (Curie and Duane[20]), or one Curie, or fractions thereof (millicurie or microcurie $\times$ $\frac{1}{10^{-6}}$). By comparison of the apparatus with standard radium solutions, or indirectly by computation, the Mache units can always be found (1 Mache unit = 37.7×10^{-10}

20. Curie and Duane, cited by Ebler, E.: Ztschr. f. anorgan. Chemie, 1911, lxxii, 243.

Curie). The substitution of a scientific measure by a term selected in memory of a celebrated person may be justified as a reason of acknowledgment, but it presents certain inconveniences; it is preferable, therefore, to use mathematical measures whenever they are possible. It has been suggested (Engler and Sieveking[21]) to adopt as unit the electromagnetic amount of the current, and by multiplication of the figure found by one billion (10^{12}) to avoid small figures.

TABLE 3.—Test of No. 13, Hot Sulphur Spring. Temperature 99.4 F. per 1,000 c.c.

Time Min.	6		7		8		9		10		11	
	Volts	M. U.	Volts	M. U.	Volts	M. U.	Volts	M. U.	Volts	M. U.	Volts	M. U.
½	139.6	1.77	.....	.....	8,013.2	101.88	6,950.7	88.81	2,733.2	34.7	..	....
1	109.6	1.39	159.2	2.02	5,013.2	63.67	4,010.7	51.47	1,713.2	21.8	96	1.22
1½	67.6	0.86	.....	.....	4,893.2	62.14	.....	.....	1,213.2	15.4	..	....
2	46.6	0.59	45.	20.57	3,893.2	50.71	2,300.7	30 90	.....	....	36	0.46
2½	46.0	0.58	.....	.....	4,269.2	54.22	2,006.7	26.02	.....	....	..	....
3	49.6	0.63	22.2	0.29	3,673.2	46.65	1,850.7	23.94	693.2	8.8	16	0.20
4	33.1	0.42	21.2	0.27	2,563.2	32.55	1,530.7	19.85	.....	....	6	0.07
5	29.2	0.37	12.8	0.16	2,253.2	28.62	1,214.7	16.96	477.2	6.1	48	0.61
6	21.6	0.27	.....	.....	2,043.2	25.95	1,010.7	13.37	.....	....	..	....
8	20.3	0.26	.....	.....	1,690.7	21.47	755.7	10.13	.....	....	..	....
10	14.8	0.19	6.2	0.08	1.521.3	19.32	686.7	8.50	297.2	3.8	54	0.69
12	8.0	0.10	.....	.....	1,318.2	16.74	.....	.....	.....	....	..	....
15	13.2	0.17	3.6	0.05	1,113.2	14.14	450.7	6.25	237.2	3.0	52	0.66
20	11.3	0.14	0.5	0.01	930.2	11.81	362.7	5.14	192.2	2.4	..	....
30	8.0	0.10	.....	.....	633.2	8.04	282.7	3.89	.....	....	..	....

EXPLANATION TO TABLE 3

6. Air in the bath-cell; values if only the air in the tank is considered without the determination of the radio-activity absorbed in the tank water.
7. Radio-activity of dry residue obtained after evaporation of 1,000 c.c. of mineral water.
8. Hot Sulphur Springs: Field test of radio-activity per 1,000 c.c.
9. Test of water determined at the laboratory, after collection of water under all precautions, and under minimal loss of time. Transport of water from spring to laboratory in a well closed glass jar, emphasizing the importance of using the water directly at the spring itself.
10. 1,000 c.c. of the same water are allowed to stand over night, and about fourteen hours later the test is carried out; considerable loss is noted.
11. Determination of radio-activity in dry evaporated residue obtained from 1,000 c.c. of Hot Sulphur Spring water.

With regard to the unit to be used in gases, no international unit has been adopted as yet. Several authors (Sommer,[12] Engler and Sieveking[21]) reject the Mache unit as unsuitable. They suggest to simply use the strength of the saturation current in electrostatic or electromagnetic units, or with the proper mention of the apparatus used, to quote simply the loss of volts per hour, or, still better, the number of ions as contained by dividing the saturation current by the amount of electricity carried by an electron (1 c.c. equals 242 ions).

21. Engler and Sieveking: Ztschr. f. anorg. Chemie, 1907, p. 53.

Further, according to P. Curie and Laborde,[22] the milligram minute has been chosen as the unit for the radio-activity of springs. (One milligram minute equals 141 Mache units; one milligram second 2.6 Mache units, Engler and Sieveking, Loewenthal.)

For sediments the factor with which the loss of volts has to be multiplied is smaller. This is based on the experience, that, according to humidity, porosity, etc., of the substance to be examined, the loss of emanation is considerably smaller.

TABLE 4.—TESTS MADE ON MAGNESIA SPRING, TEMPERATURE 98.2 F.

Time Min.	12		13		14		15		16		17	
	Volts	M. U.	Volts	M. U.	Volts	M. U.	Volts	M. U.	Volts	M. U.	Volts	M. U.
½	14,746.9	188.29	2,135	27.11	506.7	6.44	.....	....	4,807.8	61.04	2,108.9	26.78
1	20,546.9	260.945	1,175	14.92	1,694.1	21.52	93.2	1.17	11,970.3	151.01	1,808.9	21.96
1½	7,586.9	94.25	775	9.84	1,300.7	16.52	.....	....	8,674.1	111.29	1,188.9	20.60
2	5,956.9	75.65	650	8.26	931.6	11.93	168.2	2.14	7,326.6	93.05	998.9	12.69
2½	4,954.9	62.96	.....	.....	1,215.1	15.43	.....	....	5,745.4	62.97	.....	.....
3	4,306.9	54.70	425	5.40	1,086.5	13.75	103.2	1.31	5,698.6	72.37	818.9	10.40
4	3,304.9	41.98	307.5	3.91	889.8	11.30	100.7	1.28	4,779.8	60.7	818.9	10.40
5	2,734.9	34.73	269.0	3.41	846.6	10.75	85.2	1.08	4,122.9	52.36	800.9	10.17
6	2,276.9	28,92	240.0	3.05	652.3	8.28	.....	....	3,829.8	48.64	828.9	10.53
8	1,771.9	22.50	173.7	2.11	664.5	8.44	66.2	0.84	3,242.9	41.19	811.4	10.30
10	1,468.9	18.66	149.0	1.89	608.4	7.73	.....	....	2,833.7	36.99	806.9	10.25
12	1,266.9	16.09	.....	....	575.2	7.31	.....	....	2,553.2	32.42	773.9	9.83
15	1,008.9	13.96	.....	....	521.2	6.62	61.2	0.78	2,308.6	29.32	744.9	9.46
20	989.9	12.57	.....	....	469.5	5.95	.....	....	2,062.7	26.1	761.9	9.58
30	688.9	8.75	.....	....	467.7	5.84	.....	....	770.9	9.79	*	.....

* Value for water alone, as in the determination of the gas alone, the leaflets of the fontactoscope fell together and the reading could not be carried on further.

EXPLANATION TO TABLE 4

12. Field test carried out immediately at the spring, avoiding any loss of emanation.
13. Water collected under all precautions, but examined at the radiological laboratory at the Bath-house after about 4½ minutes had passed until the first reading could be made; a considerable difference in the readings is noticed. Added to this must be the time of shaking the tank, the charge of the electroscope with positive electricity (beta-rays). The first reading in No. 13 resembles that made 6 minutes after the beginning of Experiment 12.
14. Determination of gas absorbed directly over the spring; about 2,000 c.c. gas with 1,020 c.c. water contained in the tank (values for gas and tank water combined).
15. Radio-activity in dry residue from mineral water, 1,000 c.c.
16. Emanation collected from 1,000 c.c. of mineral water after heating 1,785 c.c. of gas and 1,100 c.c. of remaining tank water (values combined from both determinations.)
17. Magnesia Spring determination of gas radio-activity alone, showing always a smaller amount than found in the tank water (compare with No. 16).

DISCUSSION OF RESULTS

With regard to the frequency of radio-activity in water and the recommendation of such waters for therapeutic purposes, where the content of radio-active substances is small in waters having any action

22. Curie, P., and Laborde, cited by Engler and Sieveking (Footnote 21).

whatsoever, von Noorden's suggestion is justified, i. e., a classification of such springs as follows:

1. Weak radio-active waters containing between 25 and 50 Mache units per liter and per hour (1,250 to 2,500 × 10^{-11} gram radium).
2. Medium radio-active waters, from 50 to 100 Mache units per liter and per hour (2,500 to 5,000 × 10^{-11} gram radium).
3. Strong radio-active waters, from over 100 Mache units per liter and per hour or over (5,000 × 10^{-11} gram radium).

TABLE 5.—TESTS OF HEALING SPRINGS. TEMPERATURE 87 F.

Time Min.	18		19		20		21		22		23	
	Volts	M. U.	Volts	M. U.	Volts	M. U.	Volts	M. U.	Volts	M. U.	Volts	M. U.
½	5,482	60.62	543.9	6.91	.....	....	276.6	3.51	.....	.....	6,332.2	80.42
1	3,982	50.57	397.3	5.04	259.4	3.29	126.6	1.61	1,050.0	13.33	4,096.4	52.03
1½	3,522	44.73	260.8	3.32	.....	....	.....	....	.....	.....	.....	.....
2	2,902	36.87	.....	....	99.4	1.26	111.6	1.42	681.9	8.71	2,335.2	29.66
2½	2,506	31.83	254.5	3.23	.....	....	.....	....	518.2	6.58	.....	.....
3	2,262	28.73	250.3	3.18	159.4	2.02	66.6	0.84	542.5	6.89	1,953.8	24.81
4	1,905	23.71	182.0	2.31	174.4	2.21	66.6	0.84	331.6	4.21	1,540.4	19.68
5	1,534	19.48	172.6	2.09	195.4	2.47	.....	....	432.9	5.50	1,305.2	16.58
6	1,322	16.79	129.5	1.80	139.5	1.80	66.6	0.84	390.5	4.96	.....	.....
8	1,102	14.00	102.3	1.30	.....	....	.....	....	142.8	1.70	832.4	10.57
10	962	12.09	71.4	0.89	141.4	1.80	54.6	0.60	351.0	4.56	811.0	10.30
12	.....	.....	.....	....	.....	....	.....	....	.....	.....	.....	.....
15	674	8.56	48.4	0.61	103.4	1.31	56.6	0.72	.....	.....	.....	.....
20	550	6.99	46.4	0.59	99.4	1.26	.....	....	.....	.....	.....	.....
30	424	5.38	.....	....	.....	....	.....	....	.....	.....	.....	.....

EXPLANATION TO TABLE 5

18. Field test immediately at the spring.
19. Sample of water taken to the laboratory at Hot Springs under observation of all precautions (lapse of time about one hour; return by automobile). A great difference will be noticed between Nos. 18 and 19.
20. Sample of water determined next day, still radio-active but less than previously.
21. Radio-activity of dry residue obtained by slow evaporation of 1,000 c.c. of mineral water.
22. Gas determination collected right over reservoir; a thunderstorm and dampness interfered with the test, so only emanation as absorbed in the tank could be ascertained.
23. Dissolved emanation driven out by heat from one liter of water (gas and tank water radio-activity combined).

Our results compare favorably with the reports of Boltwood[23] from Hot Springs, Ark., and with those of Schlundt and Moore[18] from Yellowstone Park. Boltwood examined the waters five to six days after they had been collected and from his figures he calculates the initial radio-activity, based on the loss of activity, a radio-active solution must show after a given lapse of days. Although we have to deal with a theoretical value, which may differ from the radio-activity found immediately at the spring itself, Magnesia Spring (280 M. U.)

12. Boltwood: Am. Jour. Sc., 1905, xx, 128.

compares favorably with Boltwood's spring 70 C. (265.6 M. U.). In considering only the emanation as contained in the water, we determined quite a number of strong radio-active springs at Hot Springs, Va.; namely: Open well (156.6 M. U.; Thermalwater (112.5 M. U.); Swimming pool (109.27 M. U.); Hot Sulphur Springs (101.86 M. U.). In Hot Springs, Ark., only one other spring, 74 D., is marked with 106.8 M. U.

TABLE 6.—TESTS OF WARM SPRINGS. TEMPERATURE 97.0 F.

Time Min.	24		25		26		27		28	
	Volts	M. U.	Volts	M. U.	Volts	M. U.	Volts	M. U.	Volts	M. U.
½	7,537.4	95.73	1,001.4	12.72	2,551.9	32.41	11,533.1	146.47	462.0	5.87
1	6,517.4	82.77	641.4	8.13	1,118.0	14.2	5,732.1	72.80	312.0	3.96
1½	5,397.4	69.55	421.4	5.35	853.0	10.83	4,747.1	60.29	202.0	2.56
2	4,297.4	54.58	371.4	4.72	793.5	10.08	5,513.6	70.02	252.0	3.20
2½	3,745.4	47.57	.....	....	598.4	7.60	4,636.8	58.89	198.0	2.51
3	3,297.4	41.88	241.4	3.07	592.6	7.53	4,404.8	55.94	202.0	2.56
4	2,467.4	31.34	213.9	2.72	375.7	4.77	3,866.6	49.11	192.0	2.44
5	2,077.4	26.38	167.4	2.13	345.3	4.40	3,066.9	26.25	192.0	2.44
6	1,767.4	22.45	.....	....	286.3	3.62	1,837.6	23.90	177.0	2.25
8	1,424.9	18.10	.....	....	202.1	2.58	1,696.9	21.55	154.5	1.96
10	1,189.4	16.11	98.4	1.25	140.1	1.78	1,468.8	18.65	129.0	1.64
12	1,027.4	13.05	.....	....	187.1	2.38	1,880.7	23.88	.....	....
15	853.4	10.83	59.4	0.75	94.4	1.20	2,280.9	16.27	102.0	1.29
20	661.4	8.41	53.4	0.68	102.8	1.31	1,037.24	13.17	.....	....
30	487.4	5.19	.....	....	.....	....	.....	.....	.....	....

EXPLANATION TO TABLE 6

24. Radio-activity for 1,000 c.c. per one hour carried out at the brim of the swimming-pool.
25. Collected under all precautions and taken to the laboratory at Hot Springs; examination made early next morning. Similar to the experience at Healing Springs; a considerable difference between Tests 24 and 25 will be noticed.
26. Radio-activity of gas escaping from pool in 2,020 c.c. of gas mixture and in remaining tank water (476 c.c.) tank air (values combined). The test could be continued for only 20 minutes on account of meteorological conditions; beginning thunderstorm and excessive humidity, causing discharge of leaflets.
27. Dissolved emanation obtained by boiling 1,000 c.c. of pool-water, tested in 1,900 c.c. of air and 1,000 c.c. of tank water, both values combined. Leaflets of electroscope separate only slowly; small amount of emanation in air; moist atmosphere, previous to thunderstorm; a high normal loss of ionization for the air; the results are relatively low as compared with more favorable weather conditions.
28. Radio-activity of dry sediment from 1,000 c.c. of mineral water from swimming pool.

N. B.—In the tables above the figures for the radio-activity expressed in Mache units contain only two decimals, whilst in the original computation five to six decimals are quoted.

Five springs in Hot Springs and Warm Springs and Healing Springs belong to the medium strong radio-active waters, namely: Warm Springs, 95.72 M. U.; Open Spring, 92.63 M. U.; Boiler Spring, 86.54 M. U.; Healing Springs, 69.621 M. U.; Soda Spring, 64.53 M. U.

In Hot Springs, Ark., we find three springs, namely, 63 B, 97.3 M. U.; 35 A, 65.4 M. U., and 36 A, 54.8 M. U. In Hot Springs, Va.,

two spas carry a weak emanation, that is, Clubhouse (Casino) Spring, 33.16 M. U., and Cold Spring, 31.69 M. U.

In Hot Springs, Ark., the weak springs are more numerous, namely, 30 A, 49 M. U.; 39 A, 41.6 M. U.; 69 C, 40 M. U.; 26 A, 31.9 M. U.; 66 C, 30.5 M. U.; 34 A, 29.3 M. U.; 32 A, 28.9 M. U.; 64 C and 68 C, 26.1 M. U.

TABLE 7.—TESTS OF SWIMMING-POOL AT HOT SPRINGS. TEMPERATURE 81.5 F.

Time Min.	29		30		31	
	Volts	M. U.	Volts	M. U.	Volts	M. U.
½	8,604.2	109.27	4,654.4	59.11	3,949.8	50.16
1	7,164.2	90.98	3,274.4	41.58	3,887.8	49.40
1½	5,644.2	71.68	2,014.4	38.28	2,629.8	33.40
2	4,884.2	62.03	28,884.4	36.91	1,999.8	25.12
2½	4,212.2	53.49	2,398.4	30.56	1,813.8	23.04
3	3,784.2	40.06	2,194.4	27.87	1,589.8	12.19
4	3,099.2	39.36	1,849.4	23.49	1,249.8	15.87
5	2,568.2	32.61	1,606.4	20.30	961.8	12.31
6	2,224.2	28.25	1,364.4	17.33	859.8	10.92
8	1,794.2	22.79	1,129.4	14.34	664.8	8.44
10	1,494.2	18.98	1,048.4	13.32	445.8	5.66
12	1,294.2	16.43	914.4	11.61	379.8	4.82
15	1,140.2	14.48	842.4	10.69	297.8	3.78
20	930.2	11.81	*	.....	.....	....
30	730.2	9.27	.....	.....	.....	....

* Apparatus discharged automatically (so probably the water remaining in the swimming-pool would lose in activity as shown by comparison between inflow 471,698,103.925 and outflow 189,869,380.76=281,828,272.265 Mache units through a surface of 234.6975 m². Compared with this the swimming-pool for men at Warm Springs, corresponding to a radius of 20 feet (6 meters), and a depth of 6 feet (1.8 meters), corresponding to a cubic content 205,555.032 liters at 134 Mache units 27,544,374.288 Mache units. In that instance the outflow could not be measured on account of the inaccessibility of the outflow.

EXPLANATION TO TABLE 7

Probable loss in emanation per 1,000 c.c. as difference from inflow and outflow per hour, 45.9 per cent. (1 minute reading, maximal value). Measurements of swimming-pool 85.5x30.5 feet, with depth (inclined) from 3 feet 9 inches to 7 feet, or in metric square surface, 234.6975 m². Cubic measure, 43,714.6875 cubic meters, or 43,174,687.5 liters. The maximal radio-activity would amount to 471,698,103.025 Mache units. The outflow contains as maximal value, 50.1625 Mache units.

29. Radio-activity of inflow to swimming-pool, test carried out immediately at the pool, per 1,000 c.c. and per hour.

30. Outflow per one hour and 1,000 c.c. The readings could only be made for fifteen minutes, as then the surrounding air charged with emanation, caused the leaflets of the instrument to collapse.

31. Difference between inflow and outflow per 1,000 c.c. of water and one hour, continued for fifteen minutes only, due to the cause stated above.

Three springs in Hot Springs are below 25 M. U., namely, 102° T. Spring with 15.79 M. U.; Spout Spring, 16.55 M. U., and Octagon Spring, 4.88 M. U. Thirty-two springs in Hot Springs, Ark., and all the springs recorded by Schlundt and Moore in Yellowstone Park

must be considered as very weak radio-active waters. So far as known no quantitative analyses of Saratoga Springs nor of White Sulphur Springs have been published.

The waters of Hot Springs, Va., compare favorably with European springs (Sommer[24]). Among the strongest radio-active springs of the world are Brambach (1,950 M. U.); Joachimsthal (Wernerlaufstollen, 600 M. U.); Lacco Ameno (Ischia, 325 M. U.); Hot Springs, Ark., 70 C. (265 M. U.), and Magnesia Springs, Hot Springs, Va. (260.9 M. U.). The Open Well at Hot Springs, Va. (156.6 M. U.) compares with Gastein Grabenbäckerquella (155.9 M. U.), Thermalwater, Swimming Pool, Hot Sulphur Springs, Warm Springs, Open Spring, are a little lower than Landeck (Silesia) 119.8 M. U.) and higher than the spas of Carlsbad. Boiler Spring can be compared with Gastein (Chorinskiquelle, nördlich, Stollen 85.8 M. U.), Healing Springs with Gastein, Rudolphsstollen (68.8 M. U.); also Soda Spring (64.53 M. U.) with Gastein, Franz Josephs Stollen, Hinter Quelle. The Clubhouse Spring and Cold Spring of Hot Springs, Va., are a little higher than Carlsbad Mühlbrunnen, and Gastein Doctorquelle higher than Kreuznach (27.9 M. U.) and Nauheim (25.4 M. U.).

If we take into account the gas escape, the value of these mineral waters is necessarily increased, so that in bath-rooms where the atmosphere is necessarily loaded with emanation the patient must of course be benefited by such a combination. In some instances the radioactivity of the gas seems more considerable than that found in the water (Octagon Spring 102 T. Spring). The water applied in full baths owing to its radio-activity, must enforce the thermic action, and, as seen from the tables, the emanation so administered equals 4-56,000 M. U., which are doses that are usually expected from the higher radioactive European spas. If we use in our technic for the determination of the radio-activity of mineral waters the violent shaking of the water in the tank in order to free the emanation from the fluid, if, further, we know that the spraying of these waters against any obstacle also sets free the emanation, theoretically it may be presumed that half-baths, showers in any form with the mineral waters used at the bath-house set free a considerable amount of emanation, which, besides the stimulating effect on the nerves and vessels of the skin, must be inhaled by the patient. Our personal observation and experience on patients demonstrated the overstimulation of too violent procedures, which undesirable effects required several days to disappear.

Attention may be directed toward the favorable combination treatment in the pools at Warm Springs, where several millions of Mache units are contained in the water (corresponding to about 13 mg. of

24. Sommer: Emanation and Emanationstherapie, Radioactivität d. Heilquellen.

radium), and in the swimming-pool in the bath-house at Hot Springs (with about 407 millions M. U., corresponding to about 203 mg. of radium). To the thermic action of the water is added the necessity to move, to swim, the continuous emanation escaping from the large surface of water, which the patient with his mouth close to the surface of the water must necessarily inhale. So far as could be learned, the patient seems to derive more rapid and more lasting benefit from the swimming-pool treatment. Although there seems to be present in most of the mineral waters examined a small amount of radio-active sediment, our observations emphasize the fact that the mineral waters to exert their beneficial effect must be consumed right at the spring, and that without incurring any loss of time or loss of emanation. Further, a number of observations have indicated that the air surrounding the different mineral springs contains emanation, so practically the patients are continuously exposed to such a natural emanatorium, which, during long periods of time, must contribute to the final therapeutic result.

In our study no qualitative tests were carried out to ascertain the presence of the rarer gases, helium, actinium, nor thorium emanation. From the curves, however, it would seem that the continuous and rapid fall of the leaflets of the electroscope speaks in favor of more thorium than radium emanation. For this reason it would be advisable to use the water as fresh as possible for drinking purposes. To judge from the temperature of the water and from its radio-activity, there is no relationship to be ascertained, nor would the chemical analysis allow any deductions, as to the relation between a definite amount of chemical constituents in solution and the amount of radio-active substances found.

Just as for the European spas, the high amount of radio-activity found in the spas of Carlsbad, Gastein, etc., explained to a certain extent the favorable therapeutic results in gout, chronic and subacute rheumatism and in metabolic diseases, we may infer also that for Hot Springs the high radio-activity of its waters must contribute to the favorable results observed in these diseases. The remarkable improvement in certain skin diseases observed at Hot Springs is not explained by the chemical composition only; here, too, we must attribute some effect to the radio-emanation, for the expression "eliminative effect" can only be rational if these radio-active waters are taken internally; but we have observed cures of various cutaneous disorders from the exclusive external use of the waters. With regard to the indications and contra-indications of radiotherapy in medicine, we refer to our paper.[25]

25. Zueblin, E.: The Present Status of Radioactive Therapy in Medicine, Maryland Med. Jour., 1914, No. 5; ibid, 1914, No. 6.

A STUDY OF DIFFERENT NITROGENOUS DIETS IN CHRONIC NEPHRITIS *

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The object of this study has been to note the effect of diets containing different amounts of nitrogen on cases of chronic nephritis. To study this effect, attention has been paid especially to the different tests devised in recent years to show renal function, to the blood-pressure, and to the general condition of the patient.

Many articles have appeared in medical literature concerning the value and effects of different types of diets in chronic nephritis. No attempt will be made to review those articles which deal with the effect of diets on the general condition of the patient, nor shall we take up the literature which deals with the effect of diets in which other food elements than the nitrogen have been varied. In a study on nephritis in 1905 Widal[1] and Javal among other points showed that the urea of the blood became elevated in certain types of chronic nephritis when increased nitrogen in the food was consumed, or when urea was added to the diet. In 1913 Goodall[2] declared that the blood-pressure fell in chronic nephritis when the patients were placed on a low protein diet. In one case he found the non-protein nitrogen of the blood low after the low diet, and concluded that the general condition and blood-pressure were dependent on the presence of the end-products of protein metabolism in the blood. Seymour[3] in 1913, and Folin, Denis and Seymour[4] in 1914 reported on cases of chronic nephritis given diets containing average, high, and low amounts of protein. No accurate record was mentioned of the amount of the diet refused by the patient. They found that the patients on the high diet did not seem so well, and that the non-protein nitrogen of the blood could be increased or lowered by the diet. They found no relation between the blood-pressure and the nitrogen retention and no relation between

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* From the Department of Medicine, Harvard University, and the Medical Clinic of the Peter Bent Brigham Hospital.

1. Widal: La Semaine méd., 1905, xxv, 313.
2. Goodall: Boston Med. and Surg. Jour., 1913, clxviii, 761.
3. Seymour: Boston Med. and Surg. Jour., 1913, clxix, 795.
4. Folin, Otto, Denis, W., and Seymour, Malcolm: The Non-Protein Nitrogenous Constituents of the Blood in Chronic Vascular Nephritis (Arteriosclerosis) as Influenced by the Level of Protein Metabolism, THE ARCHIVES INT. MED., 1914, xiii, 224.

the phenolsulphonephthalein elimination and the non-protein nitrogen of the blood when the latter was varied by the diet.

The numerous observations from which this paper is compiled were made for the most part by one or the other of us. In some instances, however, the records of the Peter Bent Brigham Hospital were used. During the time the work was in progress frequent comparisons were made between our figures and those of the hospital physicians, so that we feel no hesitancy in using their figures when it is necessary.

Any one who has worked on a problem quantitatively in a general hospital will realize the possibilities of error that readily creep in. Careful supervision of the work in these experiments makes us feel that although an occasional error may have produced some unexpected result, the figures as a whole are relatively accurate. Of course, we should not draw any conclusions from a single observation in this kind of work.

For these studies three different types of diets were selected. They all contained as nearly as possible the same number of calories and the same amount of sodium chlorid. In addition to the salt in the food enough was added in the cooking to bring the total up to approximately 4 gm. a day in each diet. One diet, called the standard nephritic diet, contained about 73 gm. of protein daily. Another, called the high protein contained about 149 gm. of protein daily, and the third, called the low protein diet, contained about 26 gm. of protein daily.

For our estimations it was assumed that if the amount of protein was divided by 6.5 the result would show the number of grams of nitrogen. Thus the high protein diet contained practically 23 gm. of nitrogen, the standard diet 11.2 gm., and the low protein about 4 gm. of nitrogen daily.

The hospital dietitian, Miss McCollough, spent considerable time in endeavoring to make up meals which contained these amounts of protein and sodium chlorid in the twenty-four hours, and which would be palatable and variable from day to day. We take pleasure in this opportunity to extend to her our thanks. The figures for values of raw food were taken from the United States government bulletin, for cooked food from Locke's[5] tables. In the high protein diet it was necessary to increase the caloric value from the usual 2,100 to 2,600 in order to make the meals palatable.

As many of the studies could not be carried out completely owing to the patients leaving the hospital or to other causes, we shall have to report some cases in which only certain points have been brought out. The plan followed when possible consisted in letting the patient rest for a few days after entrance to the hospital on a simple light diet.

5. Locke: Food Values, D. Appleton & Co., 1911.

After the patient had become used to the new surroundings, the standard nephritic diet was started and an accurate record kept of the amount of protein eaten at each meal. While the patient was on the standard nephritic diet, on one day 10 gm. of sodium chlorid, on another 20 gm. of urea were added to the diet, in order to study the ability of the kidneys to excrete those substances. Widal[6] has divided nephritis recently into those cases which are unable primarily to excrete sodium chlorid and those that are unable to excrete non-protein nitrogen. Schlayer[7] and Monakow[8] have suggested the foregoing two tests to show the kidneys' ability in regard to salt and nitrogen.

After the patient had been on the standard nephritic diet for a few days the amount of non-protein nitrogen in the blood was determined and the phenolsulphonephthalein excretion test done. The patient then was placed on the high protein diet for a few days and these two tests repeated, then on the low protein diet for a similar period and the tests were done again. The amount of fluid intake and output was recorded as was also the specific gravity of the urine. The amount of nitrogen and salt excretion during many of the experiments was studied throughout, while in others only in part. Blood-pressure observations were made from time to time.

The amount of the non-protein nitrogen in the blood and the power to excrete phenolsulphonephthalein were taken as the two most comprehensive single tests for renal function at the present time. Recent work on these tests by us[9] has shown that the two tests in general parallel each other, although there may be considerable variation in the phenolsulphonephthalein excretion because of passive congestion or other unknown causes, in cases in which the blood nitrogen remains constant. Our feeling is that the amount of non-protein nitrogen in the blood is slightly the more reliable test of the two. By the methods used for determinations the normal amount of non-protein nitrogen in the blood is between 20 and 30 mg. per hundred c.c. The normal excretion of phenolsulphonephthalein in two hours is more variable, but roughly from 50 to 70 per cent.

The following methods were used for making the different determinations, and references are given to the description of the technic by the originators of the tests. As no modifications were employed, we shall not give a description of the technic. For determinations of the non-protein nitrogen of the blood we used the Folin and Denis[10]

6. Widal: Mouvement méd., 1913, i, 1.
7. Schlayer and Takayasu: Deutsch. Arch. f. klin. Med., 1910-1911, cl, 333.
8. Monakow: Deutsch. Arch. f. klin. Med., 1911, cii, 248.
9. Frothingham and Smillie: THE ARCHIVES INT. MED., 1914, xiv, 541.
10. Folin and Denis: Jour. Biol. Chem., 1912, xi, 527.

method. The method originally described by Rowntree and Geraghty[11] for the elimination of phenolsulphonephthalein was used. The nitrogen in the urine was determined by the method devised by Folin and Farmer,[12] and the sodium chlorid by the method suggested by Harvey.[13]

It seems most satisfactory to present the data on the individual cases in the form of tables and follow each table by a short description

TABLE 1.—DATA OF PATIENT 1078

Date	Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Gravity	Intake gm.	Output gm.	Intake gm.	Output gm.			
May										
12	1,500	985	1.016	11.0	7.6	4.0	2.8	20.0	54	128- 80
13	1,350	1,200	1.012	11.2	7.5	*14.0*	2.5	....	..	145- 98
14	1,500	730	1.016	11.2	6.5	4.0	3.6			
15	1,360	1,470	1.012	11.2	9.0	4.0	2.6	....	..	150-105
16	1,375	1,040	1.016	11.2	8.3	4.0	2.4			
17	1,635	1,440	1.013	*21.2*	10.5	4.0	2.6			
18	1,590	1,260	1.013	11.2	8.0	4.0	2.4			
19	1,610	900	1.016	11.2	7.6	4.0 10 KCl	2.1	....	..	130- 90
20	1,580	1,190	1.014	11.2	8.0	*14.0*	3.4			
21	1,510	1,670	1.011	11.2	8.2	4.0	4.0			
22	1,505	1,440	1.013	11.2	8.6	4.0	3.4	35.2	..	
23	1,500	1,360	1.016	23.0	12.8	4.0	2.4	....	..	120- 80
24	1,500	1,640	1.018	23.0	17.7	4.0	2.1			
25	1,500	800	1.023	23.0	12.9	4.0	0.8			
26	1,500	900	1.028	23.0	15.5	4.0	1.2	....	..	120- 80
27	1,500	960	1.024	23.0	18.6	4.0	2.2	45.0	..	
28	1,500	1,130	1.022	23.0	20.3	4.0	3.3			
29	1,500	840	1.023	17.5	14.3	4.0	1.7			
30	1,500	940	1.025	4.0	11.6	4.0	1.2	....	..	125- 85
31	1,530	900	1.014	4.0	6.2	4.0	2.6			
June										
1	1,130	400+	1.016	4.0	3.7+	4.0	0.9+			
2	1,500	1,115	1.013	4.0	6.4	4.0	2.0	....	48	130- 80
3	1,500	910	1.013	4.0	5.6	4.0	2.1	26.7	..	
4	1,390	835	1.013	14.0	6.1	4.0	1.9			
5	1,350	1,265	1.014	14.0	10.9	4.0	3.3			
6	1,520	1,565	1.011	14.0	12.1	4.0	3.3	....	..	125- 75
7	1,320	890	1.015	14.0	10.1	4.0	3.2			
8	1,305	990	1.020	4.0	4.6	4.0	2.8	31.2	..	

of the points of interest in that individual case, or by any comments that seemed appropriate. Following the presentation of the individual cases we shall give a summary of the cases taken as a whole to see what conclusions may be drawn.

11. Rowntree and Geraghty: Jour. Pharmacol. and Exper. Therap., 1910, i, 579.
12. Folin and Farmer: Jour. Biol. Chem., 1912, xi, 493.
13. Harvey, S. C.: The Quantitative Determination of the Chlorids in the Urine, THE ARCHIVES INT. MED., 1910, vi, 12.

The numbers used are the medical record numbers at the Peter Bent Brigham Hospital. The figures in italic in the nitrogen and salt columns signify the days on which the sodium chlorid and urea were added to the diet.

The first group of six cases (Tables 1-6, Chart 1) show types of nephritis which were unable to put out well added salt and urea. They fall into two groups: one in which the blood nitrogen varies with the

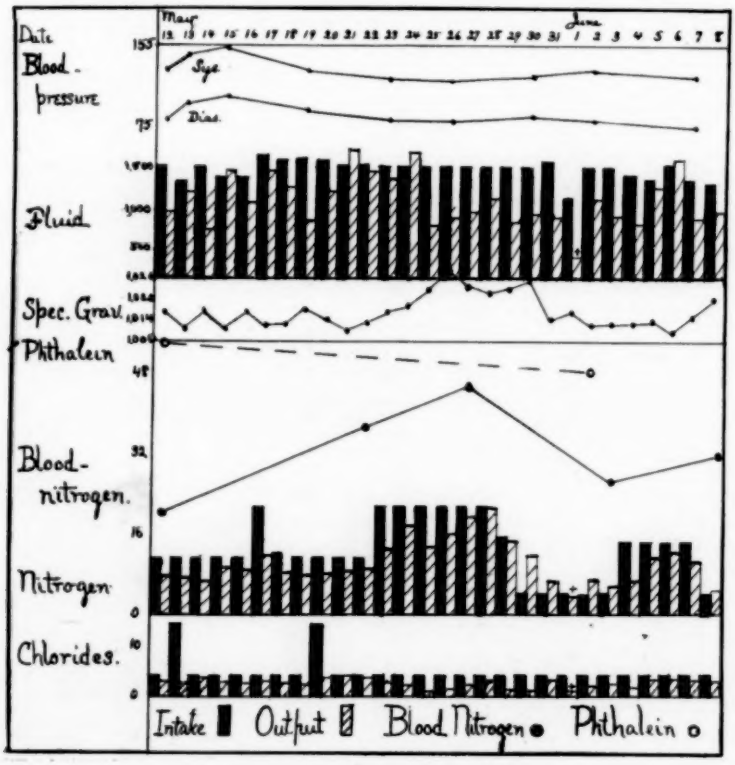

Chart 1.—Data of Patient 1078.

diet, the other in which the blood nitrogen rises despite a low protein diet.

Patient 1078 had cirrhosis of the liver with ascites in addition to a chronic nephritis. Salt and urea when added to the diet were excreted poorly. On both the standard and high protein diet the nitrogen excretion was less than the intake. The non-protein nitrogen of the blood rose steadily on both these diets and fell again on the low protein diet.

On June 4 for four successive days 20 gm. of urea were added to the low protein diet with a slight rise in the blood nitrogen. Only two phenolsulphonephthalein observations were made during this study, and they were practically the same. The blood-pressure did not show any appreciable changes with these variations in diet. On the high protein diet the patient did not feel as well as when on the other diets and had slight nausea. Ten gm. of potassium chlorid were not excreted any more readily than the sodium chlorid.

TABLE 2.—DATA OF PATIENT 624

Date	Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Gravity	Intake gm.	Output gm.	Intake gm.	Output gm.			
Dec.										
17	.....	.....	.....	....	....	10.0	8.4			
18	.....	.....	.....	....	....	10.0	10.8			
19	.....	.....	.....	....	....	10.0	11.4	....	..	230-125
20	.....	1,300	.....	11.2	11.6	*14.0*	8.9			
21	1,100	1,100	.....	11.2	11.7	4.0	6.7			
22	950	900	.....	11.2	11.0	4.0	5.7	25.4	45	225-124
23	1,300	900	.....	11.2	14.2	4.0				
24	1,250	1,100	.....	11.2	12.7	4.0	....	....	..	215-120
25	1,300	850	.....	23.0	18.1	4.0				
26	1,150	1,150	.....	23.0	16.2	4.0				
27	1,410	1,200	.....	*33.0*	20.1	4.0				
28	1,350	1,450	.....	23.0	19.2	4.0				
29	1,700	1,300	.....	23.0	18.1	4.0	....	31.2	50	210-120
30	1,500	1,150	.....	23.0	Lost	4.0				
31	1,300	1,500	1.022	23.0	23.3	4.0	....	....	..	215-125
Jan.										
1	950	1,300	.....	23.0	24.0	4.0				
2	1,500	1,450	.....	11.2	11.2	4.0	....	36.5	..	220-120
3	1,300	850	1.022	11.2	13.0	4.0				
4	1,150	1,100	.....	11.2	12.5	4.0				
5	1,050	1,050	.....	11.2	11.0	4.0	....	....	..	210-140
6	1,700	1,450	1.022	11.2	10.0	4.0				
7	1,100	1,100	.....	4.0	9.0	4.0	....	28.5	50	
8	1,600	1,000	.....	4.0	7.2	4.0	....	....	..	210-130
9	1,650	750	1.010	4.0	5.5	4.0	....			
10	1,300	1,450	.....	4.0	...	...	....	21.1	54	

The data in this case are recorded also in Chart 1 in order to show the points more graphically.

In Case 624 accurate observations on the amount of the diet refused by the patient were not kept. Therefore we record under "intake" the amount offered. Observation in a general way made it evident that the major part of the diet was eaten. In this study the nitrogen excretion surpassed the intake on the days of standard diet and on some of the days of high protein diet. No explanation is offered for this. In this case as in the preceding one the non-protein nitrogen of the blood

rose with the high protein diet and fell with the diet poor in nitrogenous content. Also, there was no appreciable variation in the phenolsulphonephthalein output or blood-pressure during these observations. The patient had very few subjective symptoms, and no change was noted in them during the period of study.

Patient 1197 had very few subjective symptoms from the chronic nephritis except slight dyspnea on exertion and headaches. This case showed a poor ability of the kidneys to put out salt and urea when

TABLE 3.—DATA OF PATIENT 1197

Date	Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Gravity	Intake gm.	Output gm.	Intake gm.	Output gm.			
May										
16	1,175	240+	1.019	11.2	2.3+	4.0	1.0+	39.0	54	225-135
17	1,970	800	1.019	11.2	9.9	4.0	1.5			
18	1,185	855	1.019	11.2	9.1	*14.0*	2.0	....	..	210-130
19	1,940	1,160	1.018	11.2	13.6	4.0	3.2			
20	1,860	1,100	1.015	*21.2*	13.9	4.0	2.4	....	..	230-140
21	1,430	1,180	1.018	11.2	13.7	4.0	2.0			
22	1,730	1,020	1.016	11.2	10.2	4.0	1.1	....	..	215-130
23	1,865	1,015	1.016	11.2	9.0	4.0	0.6	43.1	50	
24	990	1,450	1.012	11.2	12.8	4.0 KCl 10	1.2	....	..	200-120
25	1,365	1,305	1.016	6.7	10.9	*14.0*	3.2			
26	1,465	950	1.016	11.2	10.6	4.0	1.4			
27	2,305	950	1.017	11.2	10.6	4.0	1.2	....	..	195-110
28	2,356	1,070	1.018	17.8	13.0	2.5	2.3			
29	1,940	1,220	1.015	19.8	13.5	3.0	2.5	....	..	178- 95
30	1,940	1,536	1.015	23.0	16.1	4.0	3.2			
31	1,850	1,275	1.017	22.5	13.1	4.0	4.1			
June										
1	1,800	1,320	1.014	20.5	Lost	3.5	Lost	39.6	..	180-100
2	1,760	1,600	1.011	7.0	10.6	4.0	4.5			
3	1,640	450	1.016	4.0	4.5	4.0	1.0			
4	1,640	560+	.....	4.0	Lost	4.0	Lost			
5	1,630	410+	1.010	3.6	3.0+	3.8	1.3+	25.9	..	175- 90

added to the diet. The blood nitrogen was high to begin with and remained elevated on the standard diet and the high protein diet, which were only fairly well eaten. On the low protein diet, however, the non-protein nitrogen of the blood very rapidly fell to normal. The blood-pressure in this case, with rest in the hospital and apparently irrespective of diet, fell steadily during this period of study. Only two phenolsulphonephthalein observations were made early in the study, and they showed no variation. The general condition of the patient varied very little with the change of diets, but showed a gradual improvement throughout her stay in the hospital.

Case 739, of chronic nephritis with slight subjective symptoms of hypertension, showed fair ability to put out added salt, but very little ability to put out added urea. Although the urinary nitrogen was fairly well excreted on the standard diet there was a sharp rise in the non-protein nitrogen of the blood on this diet. This was maintained but not elevated by the high protein diet, which was only fairly well eaten. On the low protein diet the blood nitrogen as in the other cases returned to normal. In this case the phenolsulphonephthalein excre-

TABLE 4.—DATA OF PATIENT 739

Date	Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Gravity	Intake gm.	Output gm.	Intake gm.	Output gm.			
Jan.										
16	2,100	1,500	.....	....	...	...	...	22.8	58	235- 95
17	1,300	1,150	1.017	10.7	8.8	...	...			
18	1,650	1,150	1.016	9.1	9.6	...	...	....	..	230- 85
19	900	700	1.021	10.8	7.0					
20	1,250	800	1.020	10.5	...	...	...	....	..	220- 85
21	1,000	1,290	1.012	*19.1*	9.8	...	...	41.0	32	
22	950	1,180	1.015	9.1	11.7	...	...	....	..	220- 85
23	1,100	580	1.019	7.6	7.3					
24	1,000	720	1.018	8.5	7.4					
25	900	500	1.020	10.7	5.0					
26	1,900	2,100	1.014	22.5	10.5	4.0	7.1	37.5	35	200- 90
27	1,100	900	.....	17.9	...	4.0	4.8			
28	1,300	1,100	.....	18.0	...	4.0	6.2			
29	1,950	1,300	.....	17.5	...	*14.0*	11.2	....	..	230-110
30	1,750	2,100	.....	17.5	...	4.0	9.7	36.5	52	
31	1,000	900	1.016	3.4	...	4.0	5.4	....	..	220-100
Feb.										
1	900	500	1.019	3.2	4.0					
2	1,500	900	.....	3.2	...	...	...	....	..	210- 85
3	1,300	750	.....	3.8						
4	1,400	1,300	.....	3.1	...	...	...	25.5	52	215- 80

tion fell as the blood nitrogen rose, but returned to normal before the blood nitrogen reached normal again. The blood-pressure and general condition in this case showed practically no variations with the changes in diet.

Case 762, of nephritis, entered with a moderate amount of edema and slightly broken cardiac compensation. The ability to put out added salt and urea was poor. The nephritis as shown by the non-protein nitrogen of the blood and by the phenolsulphonephthalein test was of a moderately severe grade. The diets were eaten extremely well. On a standard and high protein diet the non-protein nitrogen of the blood rose and the phenolsulphonephthalein elimination fell. The patient did

not seem in as good general condition at this time. On a low protein diet the blood nitrogen fell, but the phenolsulphonephthalein excretion remained the same. Then on a standard diet the blood nitrogen sud-

TABLE 5.—DATA OF PATIENT 762

Date	Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Gravity	Intake gm.	Output gm.	Intake gm.	Output gm.			
Jan.										
20	1,600	1,300	1.015	6.0	...	10.0	...	43.4	35	190-110
21	1,550	1,500	1.022	6.0	...	4.0	3.8			
22	1,500	1,580	1.018	11.2	8.0	4.0	9.2	....	..	195-125
23	2,100	1,550	1.017	11.2	9.5	4.0	9.6			
24	1,950	1,350	1.017	11.2	9.1	4.0	8.1			
25	1,500	1,300	1.016	11.2	9.3	4.0	6.8	....	..	190-120
26	1,750	1,780	1.016	*21.2*	13.2	4.0	7.5			
27	1,750	1,700	1.015	11.2	10.1	4.0	7.6			
28	1,700	1,000	1.016	11.2	7.6	4.0	4.4	50.0	..	175-110
29	2,100	1,650	1.016	11.2	11.6	4.0	7.1	....	36	
30	2,100	1,500	1.017	11.2	...	4.0	6.6			
31	1,750	1,420	1.017	11.2	...	4.0	7.5	....	..	180-110
Feb.										
1	1,950	1,500	1.015	11.2	...	4.0	5.5			
2	1,900	1,500	1.015	23.0	...	*14.0*	6.5			
3	1,950	1,550	1.017	23.0	...	4.0	5.0	47.6	26	190-120
4	2,250	2,800	1.014	23.0	...	4.0	10.2			
5	2,300	2,050	1.019	21.5	...	4.0	6.5			
6	2,100	1,900	1.017	23.0	...	4.0	5.2	56.1	..	195-130
7	2,300	1,700	1.018	4.0	...	4.0	2.4	....	18	
8	2,100	1,900	1.014	4.0	...	4.0	5.8			
9	2,100	1,900	1.016	4.0	...	4.0	5.6	....	..	180-125
10	2,300	1,300	.....	4.0	...	4.0				
11	1,900	1,650	.....	4.0	...	4.0	...	44.7		
12	1,500	1,600	1.012	4.0	...	4.0	....	....	16	180-130
13	1,500	1,150	.....	4.0	...	4.0				
14	1,390	1,100	1.015	4.0	...	4.0				
15	1,500	1,100	.....	4.0	...	4.0	...	39.8	18	
16	1,500	790	.....	11.2	...	4.0				
17	1,500	1,220	.....	11.2	...	4.0	...	....	..	175-125
18	750	700	.....	4.0	...	2.0				
19	1,500	1,100	.....	11.2	...	4.0				
20	1,500	1,700	.....	11.2	...	4.0				
21	1,500	1,170	1.017	11.2	...	4.0	...	78.6	15	170-120
22	1,600	1,120	.....	11.2	...	4.0				
23	1,500	1,490	.....	11.2	...	4.0				
24	1,500	1,700	.....	11.2	...	4.0	...	....	..	150-115
Mar.								86.0	33	
7	*									

* From Feb. 24 to March 7, diet 11.2 gm. nitrogen, 4 gm. salt each day.

denly began to rise quite markedly, and eventually the phenolsulphonephthalein excretion rose. At the same time the blood-pressure fell, and the general condition of the patient became so improved that he went home. The edema disappeared as the stored-up salt was grad-

ually eliminated. Two months later the patient reported to the out-patient department in pretty fair shape with a non-protein blood nitrogen of 46 mg. per hundred c.c. of blood. This unexpected rise on the standard diet to a higher level than formerly we cannot explain.

Case 1056 represented a severe nephritis with symptoms suggestive of pending uremia without edema. The patient did not change in condition while in the hospital and left against advice. For several days practically no diet was eaten. Added salt or urea were very poorly excreted. The phenolsulphonephthalein excretion remained only a trace throughout. The non-protein nitrogen content of the blood rose steadily even on a very low protein diet. The blood-pressure made no important fluctuations.

TABLE 6.—DATA OF PATIENT 1056

Date	Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Gravity	Intake gm.	Output gm.	Intake gm.	Output gm.			
April										
12	1,500	1,200	1.014	1.3	4.1	2.0	4.0	78.9	Trace	
13	1,500	720	1.013	1.5	3.8	2.0	2.5	....	..	210-105
14	1,900	680	1.015	1.5	5.7	2.0	2.1			
15	1,850	820	1.015	0.6	2.2	*12.0*	2.9	....	..	210-105
16	1,750	230	1.013	0.0	0.7	0.0+	0.7			
17	1,750	410	1.015	0.0	2.1	0.0+	1.6	86.9	Trace	
18	1,700	860	1.014	0.0	3.7	0.0+	2.9	....	..	200-100
19	1,100	435	1.012	*10.0*	1.8	0.0+	1.7			
20	1,700	1,230	1.014	1.8	6.4	2.0	3.6	....	..	180- 90
21	2,000	800	1.020	2.4	5.2	3.4	7.4			
22	1,500	675	1.016	2.5	4.1	3.0	1.7	129.9	Trace	
23	?	630	1.015	4.0	2.8	4.0	1.7	....	..	210-100

The next group of five cases (Tables 7-11, Chart 2) show types of nephritis which apparently can eliminate added nitrogen in the form of urea or the nitrogen of a standard diet fairly well, but which cannot put out added salt well. The non-protein nitrogen of the blood, however, becomes elevated on the high protein diet. As in the other group it returns to normal on the low protein diet.

Patient 1097 entered the hospital in poor condition and showed auricular fibrillation and extensive edema. The edema quickly disappeared with the tremendous diuresis April 23. The non-protein nitrogen in the blood was above normal on admission. Added salt to the diet on May 1 was put out very poorly by the kidneys. Added urea was put out fairly well. The output of nitrogen in the urine the first few days was in excess of the intake, which suggested a high protein intake or retention with the edema before admission. This was con-

sistent with the high non-protein nitrogen in the blood at entrance. On the standard and low protein diet the nitrogen was excreted well and the blood nitrogen dropped to nearly normal. On the high protein diet which this patient ate well the output of nitrogen in the urine did not approximate the intake so closely. During this period of high

TABLE 7.—DATA OF PATIENT 1097

Date	Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Gravity	Intake gm.	Output gm.	Intake gm.	Output gm.			
April										
20	.....	.....	.....	....	...	...	...	43.4	40	190-110
21	1,300	340	1.021	4.0	5.0	1.0	0.2	....	..	215-115
22	1,000	1,865	1.016	4.0	13.2	1.0	9.0			
23	800	5,800	1.013	4.0	7.9	1.0	38.0	....	..	215-120
24	800	1,200	1.018	4.0	4.8	6.0	8.6			
25	1,000	1,400	1.016	6.0	7.1	6.0	4.0	....	..	230-130
26	1,000	310	1.022	6.0	5.3	6.0	1.6			
27	1,000	837	1.020	6.0	8.0	6.0	2.3			
28	1,300	990	1.020	6.0	7.4	6.0	2.8	....	..	210-120
29	1,200	885	1.018	6.0	6.1	6.0	3.0			
30	1,200	1,030	1.019	6.1	8.5	6.0	4.0			
May										
1	1,500	890	1.022	6.0	7.7	*16.0*	4.5			
2	1,250	550+	1.018	6.0	3.5+	6.0	7.7+	....	..	195-110
3	1,500	700	1.019	6.0	4.7	6.0	5.5			
4	1,200	1,465	1.017	*16.0*	12.5	6.0	9.6	....	..	180-100
5	1,500	410+	1.020	6.0	2.6+	6.0	3.2+	....	51	
6	1,300	Lost	Lost	6.0	Lost	6.0	Lost			
7	1,300	840	1.018	11.2	6.4	4.0	5.2			
8	1,500	1,465	1.017	11.2	13.1	*14.0*	10.2	32.2	..	190- 85
9	1,500	980	1.020	11.2	7.0	4.0	5.8			
10	1,200	1,165	1.022	11.2	13.4	4.0	5.2			
11	1,550	950	1.022	11.2	10.7	4.0	5.0	....	51	200-100
12	1,250	1,310	1.013	11.2	8.0	4.0	3.7			
13	1,075	1,015	1.015	10.7	9.1	4.0	1.0			
14	1,100	600+	1.020	23.0	8.1	4.0	0.6+			
15	1,250	1,570	1.018	23.0	19.3	4.0	3.0	....	..	180- 90
16	1,300	920	1.021	22.5	10.6	4.0	2.2			
17	1,680	960	1.020	23.0	12.3	4.0	2.0			
						KCl 10				
18	1,550	960	1.021	23.0	9.4	*14.0*	5.7	46.3	..	
19	1,250	910	1.020	8.4	11.8	4.0	4.4	....	40	
20	1,640	650	1.020	4.0	8.9	4.0	3.4			
21	1,730	1,058	1.010	4.0	5.3	4.0	3.0			
22	1,810	980	1.012	4.0	4.6	4.0	4.0			
23	.....	.....	.....	....	...	...	...	37.2		

protein diet following the standard diet the non-protein nitrogen of the blood again rose. It took apparently a larger amount of nitrogen intake to cause an increase in blood nitrogen. Again, on May 20, when the low protein diet was given, the urinary nitrogen exceeded the intake and the non-protein nitrogen of the blood fell. During the

entire period of study the phenolsulphonephthalein excretion ranged from 40 to 51 per cent. It was higher when the blood nitrogen was lower. Ten gm. of potassium chlorid added to the diet were not excreted any better than sodium chlorid.

The blood-pressure showed some variations during the stay in the hospital, but not in any special relation to the diets. It tended to be

TABLE 8.—DATA OF PATIENT 428

Date	Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Gravity	Intake gm.	Output gm.	Intake gm.	Output gm.			
Nov.										
7	1,000	1,130	.....	8.0	7.0	6.0	10.3			
8	1,000	1,265	.....	8.0	8.0	6.0	11.5			
9	1,000	1,665	.....	8.0	6.3	*16.0*	12.3			
10	1,000	1,465	.....	8.0	6.0	6.0	10.8			
11	1,000	2,050	.....	*18.0*	14.0	6.0	16.8			
12	1,000	1,316	.....	8.0	...	6.0	10.0			
28	1,000	1,300	1.020	11.2	...	4.0	...	21.5	51	
29	1,000	900	.....	11.2	...	4.0	...	....	..	122- 80
30	1,000	900	.....	11.2	...	4.0	...			
Dec.										
1	1,000	1,050	1.020	11.2	...	4.0	...	....	..	140- 94
2	1,000	980	.....	11.2	9.7	4.0				
3	1,000	840	.....	11.2	14.2	4.0				
4	1,000	1,450	.....	11.2	15.0	4.0	...	20.2	..	136- 90
5	1,000	1,360	.....	23.0	20.6	4.0				
6	1,000	1,050	.....	23.0	19.6	4.0				
7	1,800	1,650	.....	23.0	19.0	4.0				
8	1,800	1,540	.....	23.0	17.0	4.0	...	39.1	45	140- 90
9	1,800	1,600	.....	11.2	13.0	4.0				
10	1,800	1,200	.....	11.2	14.0	4.0				
11	1,800	1,300	.....	11.2	13.4	4.0	...	....	..	140- 94
12	1,800	1,150	.....	11.2	9.9	4.0	...	28.5		
13	1,800	1,180	1.030	11.2	10.6	4.0				
14	1,800	1,090	.....	11.2	11.8	4.0				
15	1,800	1,030	1.012	11.2	9.4	4.0				
16	1,800	950	.....	11.2	7.5	4.0		....	..	142- 84
17	1,800	980	1.020	11.2	6.7	4.0	...	23.9	45	
18	1,800	1,020	.....	4.0	7.6	4.0				
19	1,800	780	1.021	4.0	...	4.0	...	....	..	142- 92
20	.....	.....	.....	4.0	...	4.0				
21	.....	.....	.....	4.0	...	4.0	...	19.6	..	

lower the longer the patient was in the hospital, despite the period of high protein diet. On leaving the hospital the patient had no edema, his general condition was improved and the auricular fibrillation persisted.

In patient 428 the amount of food actually eaten was not measured, so the amount offered is recorded. Frequent observations, however, made us feel pretty certain that practically everything offered was

consumed. This patient showed early in November an ability to put out urea when added to the diet, but not salt. As in the preceding case it was necessary to put the patient on the high protein diet in order to elevate the non-protein nitrogen in the blood. On the low protein or standard diets the nitrogen in the blood remained normal. The phenol-

TABLE 9.—DATA OF PATIENT 1154

Date	Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Gravity	Intake gm.	Output gm.	Intake gm.	Output gm.			
May										
8	2,500	2,254	1.010	11.2	13.0	4.0	10.7	30.9	45	
9	1,950	1,305	1.013	11.2	9.1	4.0	5.8	....	..	220-140
10	1,350	1,020	1.021	11.2	10.3	4.0	5.3			
11	1,500	765	1.025	11.2	6.5	*14.0*	2.4			
12	1,450	940	1.026	9.9	10.9	4.0	3.6	....	..	260-160
13	1,800	600	1.016	11.2	7.1	4.0	1.1	....	..	255-155
14	2,700	3,300	1.010	*20.7*	19.1	4.0	4.3	....	60	230-150
15	2,100	940	1.020	9.9	9.3	4.0	1.4			
16	1,900	1,830	1.017	9.7	9.3	4.0 KCl 10	0.9			
17	2,100	1,150	1.011	8.7	7.3	*14.0*	2.7			
18	1,700	1,330	1.013	20.0	8.8	2.0	4.9	....	..	220-150
19	1,650	1,245	1.013	22.5	12.0	4.0	2.8	35.1	..	
20	1,650	1,810	1.014	20.0	13.7	2.0	4.1	....	..	210-140
21	1,750	1,070	1.015	11.2	8.0	2.0	1.5			
22	1,670	965	1.015	8.4	7.8	2.0	1.0			
23	3,100	2,980	1.005	4.0	7.0	4.0	2.0	37.3	51	205-130
24	2,130	930	1.010	4.0	5.3	4.0	1.3			
25	1,910	1,165	1.010	4.0	5.9	4.0	3.0			
26	950	740	1.011	4.0	3.7	4.0	1.2	....	..	180-110
27	1,730	365	1.018	4.0	3.8	4.0	1.2	33.1		
28	1,500	650	.....	4.0	...	4.0				
29	1,700	1,100	.....	6.3	...	2.0				
30	1,300	850	.....	11.2	...	4.0	...	....	..	190-120
31	1,900	1,150	1.012	10.7	5.7	4.0	3.0	32.6		
June										
1	1,960	1,440	1.010	10.7	6.0	4.0	2.6	....	..	170-110
2	1,750	1,460	1.010	17.8	9.0	3.5	3.0			
3	1,800	1,150	1.014	18.6	9.2	3.6	2.6			
4	1,525	1,430	1.011	19.6	9.6	4.0	2.0			
5	1,825	1,530	1.012	20.5	9.2	3.5	4.6	41.3	..	150-100

sulphonephthalein excretion and the blood-pressure showed no appreciable variation with the changes in diet. By the time this study was made the patient was practically without symptoms except slight edema and remained so during the study.

Patient 1154 is again an example of a marked retention of added salt. In putting out his added urea it is interesting to note that it caused a diuresis as is frequently seen. He was also unable to excrete

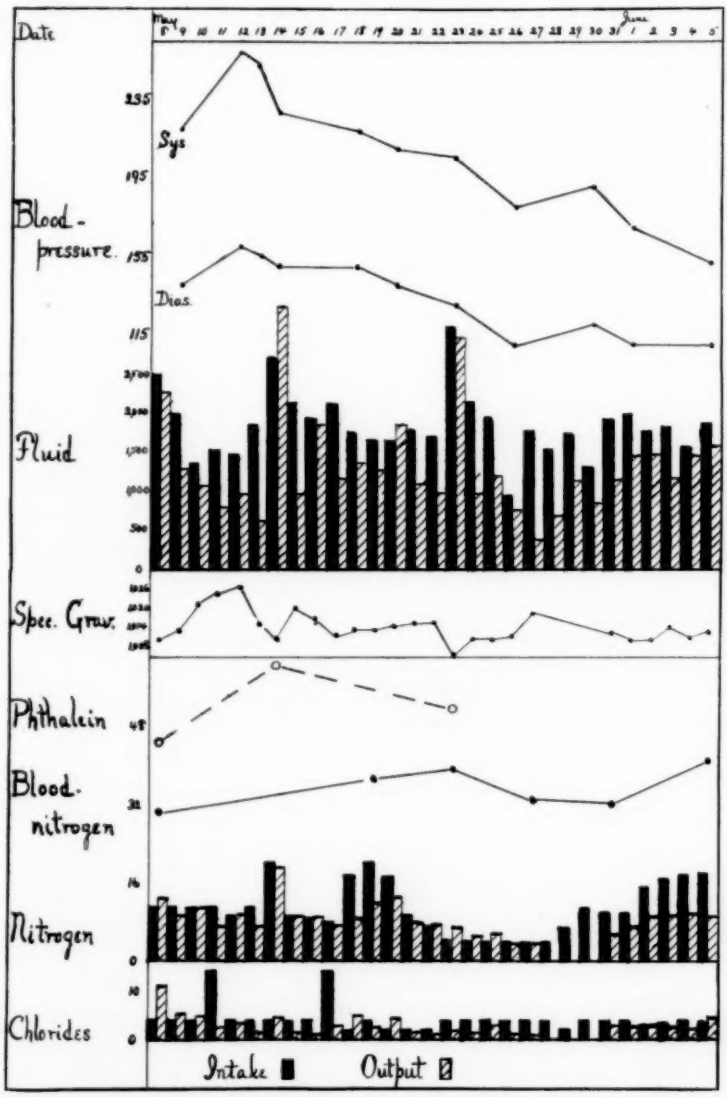

Chart 2.—Data of Patient 1154.

TABLE 10.—Data of Patient 1075

Date	Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Gravity	Intake gm.	Output gm.	Intake gm.	Output gm.			
April										
15	800	980	1.025	4.0	14.1	1.0	3.1	....	..	190-110
16	800	800	1.025	4.0	7.2	1.0	3.2	23.8	55	175- 95
17	800	645	1.026	4.0	10.0	1.0	3.0			
18	1,000	910	1.022	8.0+	8.6	3.0+	7.2			
19	1,000	1,100	1.020	8.0+	9.9	3.0+	10.5			
20	1,000	875	1.021	8.0+	7.5	3.0+	7.8	....	..	165- 90
21	1,550	1,280	1.016	11.2	7.0	4.0	8.8			
22	1,600	1,560	1.018	11.2	9.7	4.0	7.6			
23	1,600	2,340	1.014	11.2	10.5	4.0	10.2	....	..	165-100
24	1,700	2,740	1.012	*21.2*	17.8	4.0	13.0			
25	1,650	2,125	1.015	11.2	12.8	4.0	7.6			
26	1,550	1,300	1.019	11.2	7.2	4.0	8.4	20.7		
27	1,400	1,590	1.017	11.2	8.2	4.0	6.8	....	62	155-100
28	1,500	1,940	1.013	11.2	8.1	4.0	4.2			
29	1,300	1,350	1.018	23.0	18.9	4.0	3.5			
30	1,400	1,450	1.026	23.0	17.8	4.0	4.8	....	..	160- 95
May										
1	1,200	820	1.023	23.0	7.8	*14.0*	3.7			
2	1,700	1,340	1.025	23.0	15.8	4.0	7.7	....	..	140- 95
3	1,700	1,310	1.023	23.0	15.3	4.0	3.6			
4	1,700	940	1.021	23.0	12.4	4.0	2.0			
5	1,900	780	1.019	23.0	9.6	4.0	2.2	....	..	140- 95
6	1,700	1,665	1.018	23.0	20.0	4.0	2.0	36.5	45	

TABLE 11.—Data of Patient 817

Date	Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Gravity	Intake gm.	Output gm.	Intake gm.	Output gm.			
Feb.								....	..	210-140
2	.....	.....	.....	11.2	...	4.0	...	....	56	
3	2,000	1,300	1.022	11.2	...	4.0	...	31.8	..	220-145
4	2,100	700	.....	11.2	...	4.0	...			
5	1,700	850	.....	11.2	...	4.0		....	..	200-130
6	1,950	750	1.023	11.2	11.6	4.0	2.4			
7	1,900	750	1.027	11.2	12.3	4.0	1.4	30.0	53	
8	1,950	850	1.023	11.2	12.0	4.0	1.0	....	..	200-135
9	2,100	1,100	1.022	*20.2*	18.1	4.0	1.4			
10	1,950	950	1.027	11.2	15.2	4.0	1.8			
11	1,600	950	1.027	11.2	...	*14.0*	4.0	....	..	195-130
12	1,500	750	1.027	23.0	...	4.0	3.6			
13	2,000	750	1.028	23.0	...	4.0	1.2			
14	1,500	950	1.026	23.0	...	4.0	3.2	....	..	195-130
15	1,500	950	1.025	21.5	...	4.0	3.2	35.2	51	
16	1,500	1,150	1.025	18.5	...	4.0	5.4			

TABLE 12.—DATA IN CASE 1200 (CONTROL)

Date	Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Gravity	Intake gm.	Output gm.	Intake gm.	Output gm.			
May										
30	1,650	1,820	1.015	11.2	11.4	*14.0*	11.0	23.8		
31	1,460	1,700	1.016	*21.2*	20.2	4.0	5.6			
June										
1	1,350	990	1.020	11.2	13.6	4.0	2.0			
2	1,375	925	1.024	23.0	16.0	4.0	2.0	25.3		
3	950	1,020	1.020	17.8	16.0	3.0	4.0			
4	1,425	1,230	1.018	22.0	15.4	3.8	2.7			
5	1,475	2,290	1.015	22.0	18.2	3.8	11.4			
6	1,725	1,180+	1.014	23.0	10.6+	4.0	3.6+	22.4	58	
7	1,425	760	1.025	22.0	15.2	3.8	2.0			
8	1,280	1,660	1.015	10.0	...	4.0	2.2			

TABLE 13.—DATA IN CASE 1033 (CONTROL)

Date	Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Gravity	Intake gm.	Output gm.	Intake gm.	Output gm.			
April										
11	1,500	1,100	.....	11.2	....	4.0				
12	1,600	900	.....	11.2	....	4.0				
13	1,500	1,400	.....	11.2	....	4.0				
14	1,250	550	1.026	11.2	....	4.0				
15	1,300	1,150	.....	11.2	....	4.0				
16	1,500	1,150	.....	11.2	....	4.0	...	21.6	58	
17	1,650	580	.....	11.2	....	4.0				
18	1,350	1,300	.....	11.2	....	4.0				
19	1,100	900	.....	11.2	....	4.0				
20	1,650	900	.....	11.2	....	4.0				
21	1,850	500	1.018	11.2	....	4.0				
22	1,610	900	.....	11.2	....	4.0	...	17.6		
23	2,100	1,100	.....	23.0	....	4.0				
24	2,100	1,100	.....	23.0	....	4.0				
25	1,950	700	.....	23.0	....	4.0				
26	1,900	700	.....	23.0	....	4.0				
27	1,800	580	.....	23.0	....	4.0				
28	1,850	500	.....	23.0	....	4.0	...	20.6		

TABLE 14.—Data in Case 920 (Control)

Date	Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Gravity	Intake gm.	Output gm.	Intake gm.	Output gm.			
Mar.										
26	1,500	2,300	.....	10.5	....	3.8	...	....	..	125 -50
27	1,500	1,800	1.022	11.2	....	4.0	...	27.0	..	115- 50
28	1,500	1,700	.....	11.2	....	4.0	...	....	58	
29	1,500	1,450	.....	10.7	....	4.0				
30	1,500	950	.....	11.2	....	4.0				
31	1,500	1,350	.....	21.5	....	3.8				
April										
1	1,500	1,300	.....	23.0	....	4.0	...	....	..	140- 80
2	1,500	1,150	.....	22.9	....	4.0				
3	1,500	1,750	.....	23.0	....	4.0				
4	1,500	1,580	.....	21.5	....	3.8	...	26.6	..	150- 80

TABLE 15.—Data in Case 1252 (Control)

Date	Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Gravity	Intake gm.	Output gm.	Intake gm.	Output gm.			
June										
18	1,400	1,100	.....	11.2	....	4.0				
19	2,300	1,900	.....	11.2	....	4.0	...	20.1	..	150- 90
20	1,500	2,150	1.008	4.0	....	4.0				
21	2,260	1,660	1.008	4.0	4.0	4.0	3.2			
22	1,450	1,160	1.009	4.0	4.2	4.0	2.3			
23	2,100	200+	.....	4.0	....	4.0	...	19.2		

potassium chlorid any better than sodium chlorid. It was only on a high protein diet, which he ate fairly well, that the non-protein nitrogen of the blood rose, although throughout the study the blood nitrogen was on the upper border of normal limits. The phenolsulphonephthalein elimination varied a little, but not with any special change in diet. The blood-pressure showed a steady tendency to fall during the period of study, which was from the beginning of his stay in the hospital, but did not seem to bear any relation to the diets. The general condition showed slight improvement with his stay in the hospital irrespective of diet, although the albuminuric retinitis and anemia from which he suffered changed but little.

The data in this case also are recorded in Chart 2 in order to bring out the essential points more clearly.

Patient 1075 had marked edema and poor ability to excrete salt. As the salt was eliminated the edema disappeared and the blood-pressure fell steadily irrespective of the nitrogen content of the diet. The nitrogen elimination was good on the low protein and standard diets, and it was only after prolonged high protein diet, which was well taken, that the non-protein nitrogen of the blood rose. The phenolsulphonephthalein elimination fell slightly with the rise in blood nitrogen.

Case 817 is included as it shows changes similar to those in the preceding case, except that there was no edema.

The next four cases (Tables 12-15) were controls in persons, so far as we could tell, absolutely free from nephritis. Three of them were placed on a high protein diet following the standard diet, and one on a low protein after the standard diet. The diets were well taken and accurately measured. It will be readily seen that the high protein diet was taken for a considerable time without rise in the non-protein nitrogen of the blood; nor was there any appreciable drop in the patient's non-protein nitrogen of the blood after the low protein diet.

The next two cases (Tables 16 and 17) did not have the added salt and urea tests made, but seem worth recording because of the sharp rise in non-protein nitrogen of the blood, in Case 589, on a high protein diet, and in Case 785, on a diet very low in nitrogen. The latter patient died the day following the last estimation of blood nitrogen.

It would not be fair to omit the following four cases (Tables 18-21) which show varying degrees of inability to put out added salt and urea. They also show other evidences of nephritis, yet very little if any rise in non-protein nitrogen in the blood on even high protein diet. In these cases, also, there seems to be no relation between the phenolsulphonephthalein excretion or the blood-pressure and the diets. The general condition of the patients did not vary with the diets. Their symptoms

TABLE 16.—Data of Patient 589

Date	Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Gravity	Intake gm.	Output gm.	Intake gm.	Output gm.			
Dec.										
5	1,100	1,500	1.009	6.0	....	6.0	...	20.8	27	
6	1,200	1,350	.....	6.0	....	6.0	...	....	..	198-115
7	1,200	1,040	.....	6.0	....	6.0				
8	1,420	2,100	.....	11.2	....	4.0				
9	1,360	1,300	1.014	11.2	....	4.0	...	....	..	195-110
10	1,200	1,700	1.015	11.2	....	4.0	...	....	50	
11	1,200	1,500	1.018	11.2	4.2	4.0				
12	950	1,050	.....	11.2	5.3	4.0				
13	950	1,100	1.018	23.0	5.8	4.0	...	....	..	170-100
14	1,200	900	.....	23.0	8.5	4.0				
15	1,300	1,550	.....	23.0	12.1	4.0	...	43.5	24	

TABLE 17.—Data of Patient 785

Date	Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Gravity	Intake gm.	Output gm.	Intake gm.	Output gm.			
June										
5	3,145	1,840	1.009	9.2	5.1	4.0	5.1	....	0	
6	2,750	1,300	1.009	10.0	3.0	4.0	3.0	117.0	0	130- 90
7	1,305	1,220	1.007	9.8	4.0	4.0	2.8			
8	2,595	460	1.007	7.0	1.5	3.5	0.64	130.0	0	135- 95
9	1,000	450	1.011	9.2	1.3	3.5	0.72	....	..	†
10	2,700	380	.....	4.6	....	2.0	...	179.0	0	180- 80
11	2,500	150	.....	4.0	2.0					
12	1,300	0	.....	0.0	....	0.0	...	....	..	140- 65
13	Died									

† Convulsion.

TABLE 18.—Data of Patient 1072

Date	Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Gravity	Intake gm.	Output gm.	Intake gm.	Output gm.			
April										
16	1,100	1,480	1.015	10.7	3.1	4.0	7.2	....	..	190-100
17	1,300	1,100	1.010	9.7	3.0	3.0	1.2	31.8	60	
18	950	840	1.015	10.7	6.3	*14.0*	4.0	....	..	200-110
19	1,300	1,180	1.009	8.8	3.5	3.0	2.7			
20	1,300	2,400	1.010	*18.7*	8.2	4.0	6.7	....	..	210-112
21	1,500	1,810	1.010	10.7	8.0	4.0	3.2			
22	1,680	1,915	1.010	11.1	7.4	4.0	4.0	....	..	185- 95
23	1,900	1,190	1.011	10.0	4.1	4.0	4.6			
24	1,300	2,060	1.011	12.6	3.7	4.0	2.8	29.4	..	180-100
25	1,500	1,150	1.015	17.3	7.1	3.0	1.0			
26	1,300	1,630	1.012	17.3	8.2	3.0	1.9			
27	1,500	1,320	1.011	19.0	7.5	3.0	1.2			
28	1,550	2,045	1.011	20.4	7.0	3.5	2.4	....	..	185-100
29	1,400	1,565	1.012	17.0	6.0	3.0	2.0			
30	1,500	1,570	1.013	17.0	8.4	3.0	2.5	....	..	180-100
May										
1	1,350	1,630	1.012	19.7	8.1	3.0	2.0	34.0		
2	1,500	1,450	1.010	13.0	6.7	2.0	1.6	....	..	178-100
3	1,350	1,460	1.008	4.0	4.8	4.0	1.5			
4	1,200	1,092	1.010	4.0	4.6	4.0	1.9	....	..	170- 98
						KCl 5				
5	1,100	1,355	1.010	4.0	2.8	*9.0*	7.2	23.7	51	

TABLE 19.—Data of Patient 675

Date	Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Gravity	Intake gm.	Output gm.	Intake gm.	Output gm.			
Jan.										
7	1,750	1,100	1.012	4.0	....	4.0				
8	1,780	1,150	.....	4.0	....	4.0	1.9			
9	1,170	300+	.....	4.0	....	4.0	3.5	34.0	54	170-105
10	1,200	700	.....	4.0	....	4.0	2.3			
11	1,160	500	.....	4.0	....	*14.0*	6.5			
12	1,100	900	.....	4.0	4.1	4.0	5.2	....	..	145- 85
13	1,100	900	.....	4.0	4.7	4.0	4.0			
14	1,650	900	.....	8.4	4.8	3.6	...	21.6	55	
15	1,550	1,300	1.022	*21.2*	12.3	4.0	...	....	..	150- 90
16	1,550	1,300	1.016	11.2	9.2	4.0				
17	1,500	750	1.021	11.2	8.7	4.0				
18	1,520	880	1.011	7.9	7.4	3.0	...	26.3	..	145- 90
19	1,150	500	.....	6.9	....	3.0	...	....	51	
20	800	580	.....	6.8	....	3.0	...	....	..	140- 85
21	550	1,080	.....	19.8	....	3.0				
22	1,700	1,260	1.015	13.0	8.2	2.0				
23	1,100	1,020	1.012	13.0	7.0	2.0	...	....	..	145- 85
24	1,550	820	1.015	13.0	6.0	2.0				
25	950	1,250	.....	11.2	....	2.0	...	29.0	43	150- 90

TABLE 20.—Data of Patient 1029

Date	Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Gravity	Intake gm.	Output gm.	Intake gm.	Output gm.			
April										
12	900	570	1.021	11.0	3.1	4.0	2.8			
13	1,300	1.080	1.014	5.2	5.0	2.0	3.8	28.5	60	220- 95
14	1,300	430	1.020	6.7	4.0	2.0	0.86			
15	1,500	520	1.026	2.7	6.0	*12.0*	3.7	....	..	185- 90
16	1,300	305	1.021	4.0	1.8	2.0	2.4			
17	1,100	300	1.028	5.1	3.8	2.0	1.2	....	..	190- 90
18	1,300	510	1.013	*15.1*	6.2	2.0	0.9			
19	1,300	605	1.015	6.7	5.5	2.0	1.3			
20	1,100	305	1.026	6.7	5.1	2.0	0.9	....	..	185- 95
21	1,300	830	1.015	15.7	5.6	2.6	1.7	19.5	75	180- 95
22	1,300	1,010	1.013	9.7	6.0	1.8	3.0			
23	1,500	440	1.026	10.7	5.5	2.0	2.8			
24	1,300	1,115	1.020	20.0	9.0	3.8	4.2			
25	1,300	500	1.026	12.0	7.0	2.1	1.1	....	..	185- 80
26	1,300	760	1.020	14.3	8.7	2.5	2.2			
27	1,650	1,800	1.017	14.4	11.1	2.5	2.3			
28	1,600	1,270	1.020	14.0	10.8	2.5	1.1			
29	1,650	1,530	1.016	15.0	9.8	2.6	3.4	21.7		
30	1,300	1,132	1.022	15.0	11.3	2.6	2.0	....	..	205-105

TABLE 21.—Data of Patient 684

Date	Fluid Intake c.c.	Urine		Nitrogen		NaCl		Mg. N. per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24-Hr. Amount c.c.	Specific Gravity	Intake gm.	Output gm.	Intake gm.	Output gm.			
Jan.										
6	950	480	.....	11.2	....	4.0	...	35.9	65	210-100
7	700	690	.....	11.2	....	4.0				
8	1,150	300	.....	11.2	....	4.0				
9	1,250	700	.....	4.0	....	4.0	5.2	....	..	200-110
10	1,900	1,300	.....	4.0	....	4.0	3.0			
11	1,380	1,700	.....	4.0	....	4.0	3.0			
12	2,100	1,780	.....	4.0	3.2	*14.0*	6.2	....	..	220-130
13	1,150	910	.....	4.0	4.2	4.0	7.1			
14	1,900	2,100	.....	11.2	8.4	4.0	4.5	23.3	70	
15	1,900	1,700	1.015	*21.1*	16.0	4.0	...	....	..	210-110
16	1,380	1,950	1.014	11.2	12.6	4.0	...			
17	1,700	1,500	1.012	11.2	6.3	4.0	...	....	..	200-110
18	1,700	1,500	1.011	10.7	....	4.0				
19	1,650	1,900	.....	10.8	....	4.0	...	27.7	57	
20	2,000	1,590	.....	10.7	....	4.0	...	....	..	200-110
21	1,350	1,280	1.012	10.7	8.1	4.0				
22	1,300	1,100	1.019	8.2	10.8	1.5	...	....	..	180-108
23	1,650	980	1.026	21.0	17.0	3.6				
24	2,650	1,750	1.015	21.0	15.0	3.6				
25	1,650	1,620	.....	21.5	....	3.8				
26	2,100	2,300	.....	....	...	...	...	21.0	47	220-120

were slight in all the cases. In all these cases the non-protein nitrogen of the blood fell to the lower level of normal limits on the low protein diet.

In endeavoring to draw any conclusions from such a study as this or from any study of nephritis, it must be borne in mind that it is frequently impossible to decide accurately what type of nephritis from a pathological-anatomical point of view we are dealing with. In this study in most of the cases the kidneys have been studied from the point of view of their functional ability rather than with any attempt to classify the cases on an anatomical basis. The functional tests consisting in the addition of salt and urea to the diet do not permit in our series of cases such a sharp classification as Widal makes. Apparently, cases do occur in which the salt is not excreted and the nitrogen is. In the cases with a nitrogen retention, however, of our series the salt was also poorly excreted.

It is safe to say that not all of our cases of presumably the same type of functional renal disturbance act in the same way in response to the changes in diet. On the other hand, the majority of them do. Thus those cases which eliminate added urea and salt poorly tend to show an increase in the non-protein nitrogen of the blood on a diet not excessive in nitrogen, while those cases which excrete urea well but salt rather poorly, only show an increase in non-protein nitrogen of the blood on a diet rich in protein.

We find, as did Folin, Denis and Seymour, that the elimination of phenolsulphonephthalein in the urine in most of these cases of nephritis does not vary especially with the diets. In a few cases, however, it follows in a slight degree inversely to the changes in the non-protein nitrogen of the blood.

The blood-pressure did not seem to vary with the amount of nitrogen in the diet or of non-protein nitrogen in the blood as Goodall described it. It did seem to fall gradually after rest in the hospital, and especially in those cases of salt retention after the salt had been eliminated by a prolonged diet low in sodium chlorid content.

The general condition of the patient did not seem to be affected by the diets except in a few cases on the high protein diet, at which time the patients did not feel so well. This is somewhat different from Seymour's findings in which the high protein diet usually made the patients feel poorly. In his cases, however, the high protein diet was continued a longer time. The high protein diet as a rule was not enjoyed by many of the patients.

The low protein diet almost always caused a drop in the non-protein nitrogen of the blood.

Since frequently the variation in the amount of non-protein nitrogen in the blood is the only result of the changes in diet which

can be made out, the question may fairly be raised of how much value in prognosis is a rise in the non-protein nitrogen in the blood when brought about by an increased nitrogen content in the diet. Is there any appreciable change in the patient's renal condition with these changes in diet which only this test will show? These questions cannot be answered at present, but undoubtedly the diet should be considered when the amount of non-protein nitrogen in the blood is used as a basis for determining the prognosis. Presumably a rise in non-protein nitrogen in the blood in response to increased protein in the diet indicates a slighter degree of renal disturbance than is indicated by a rise when the patient is on a low protein diet.

It seems justifiable to conclude that in certain types of chronic nephritis the nitrogenous content of the diet should be carefully watched in order to prevent an increase in non-protein nitrogen in the blood. The exact effect of an increase in blood nitrogen produced by a high nitrogenous diet is not known at present, but presumably it is unfavorable to the best interests of the patient, since in some it increases their discomfort as shown by Cases 1078 and 762 of this series and cases studied by Seymour. A diet low in nitrogen content will frequently keep down to normal the non-protein nitrogen of the blood in chronic nephritis.

METABOLISM STUDY OF A CASE OF CONGENITAL HEMOLYTIC JAUNDICE WITH SPLENOMEGALY *

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I. INTRODUCTION

The interesting syndrome of chronic acholuric, pleiochromic jaundice without the usual syndrome of biliary intoxication associated with anemia and splenomegaly was first noted clinically by Murchison[1] in 1883. Minkowski[2] in 1900, however, reported a very complete study of a group of cases occurring in one family. Excellent reviews of the subject, together with the literature, have been presented by Tileston and Griffin[3] and by Thayer and Morris,[4] so we shall in this paper consider only those details which have relation to the experimental work to be described.

Besides the usual hereditary form of this disease, there is a familial type and a congenital type, in which the disease dates from birth and appears in only one of the family. It may be noted from the history that the case described in this paper belongs to this type. Another type is the so-called "acquired" form, in which the disease usually appears in childhood or adolescence.[5]

The interesting work of Whipple and Hooper[6] has placed the possibility of a purely hemolytic jaundice on a firm scientific foundation. They think it possible that the endothelium of the blood-vessels is the agent which brings about the rapid change of hemoglobin to bile-pigment, and that this mechanism comes into play when there has been a destruction of many red cells with much hemoglobin free in the plasma.

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* From the Laboratory of Dr. James P. McKelvy, Pittsburgh.

1. Murchison: Diseases of the Liver, Ed. 3, 1885, 481.

2. Minkowski: Verhandl. d. Cong. f. inn. Med., 1900, xviii, 316; Deutsch. Klin., 1905, v, 651.

3. Tileston and Griffin: Am. Jour. Med. Sc., 1910, cxxxix, 847.

4. Thayer and Morris: Bull. Johns Hopkins Hosp., 1911, xxii, 85.

5. Richards and Johnson: (Jour. Am. Med. Assn., 1913, lxi, 1586), have reported an interesting and well-studied case of congenital hemolytic jaundice. See also Pel; Deutsch. Arch. f. klin. Med., 1912, cvi, 239; Quadri; Virchows Arch. f. path. Anat., 1914, ccxv, 151, and McNee, Jour. Path. and Bacteriol., 1914, xviii, 325.

6. Whipple and Hooper: Jour. Exper. Med., 1913, xvii, 612.

Many theories have been put forth to explain this peculiar syndrome. Pick[7] thought that there was present a congenital communication between the bile passages and the lymphatics. Hayem's[8] latest view is that it is due to syphilis. Minkowski believes that it is due to a congenital perverted function of the liver cells, and on this account, the bile is excreted into the lymphatics instead of into the bile capillaries. Chauffard's[9] discovery that in this syndrome there is present an increased fragility of the red cells opened up a new path for theories. The disease could be explained on this basis: that owing to the increased susceptibility of the red cells to hemolytic agents, the anemia develops and regeneration types of red cells appear in the circulation.

This increased destruction of red cells then leads to an increased formation of bile pigment and the resulting icterus. As several have failed to find hemolysins in the blood, it may be said that the increased destruction of the red cells takes place in the spleen, which leads to an increased work of the spleen and therefore accounts for the splenomegaly. This hemolytic theory is the one generally accepted to account for the symptom-complex. Troisier thinks that the fragility of the red cells depends on the fact that they have already become sensitized by union with a hemolytic amboceptor. Hutchison and Panton,[10] in a study of a case of the "congenital" type, think that the production of the defective red cells is a factor of considerable importance in the ultimate cause of this condition. Hawkins and Dudgeon[11] are also of the opinion that the primary change lies in the blood-forming organs and not in the biliary system. Widal[12] and his school think that the red cells are destroyed in the blood and the bile pigment is formed there. The splenomegaly then results from the increased work due to bile destruction. Banti thinks the primary lesion is in the spleen. The view of Vaquez and Aubertin has found most favor. They believe the jaundice is due to the bilirubin circulating in the blood, which is pro-

7. Pick: Wien. klin. Wchnschr., 1903, xvi, 493.

8. Hayem: Presse med., 1898, vi, 121; Bull. et mém. Soc. méd. d. hôp. de Paris, 1908, Series 3, xxv, 122.

9. Chauffard: Bull. et mém. Soc. méd. d. hôp. de Paris, 1901, Series 3, xviii, 444; Semaine méd., 1907, xxvii, 25; Presse méd., 1907, xv, 345; Bull. et mém. Soc. méd. d. hôp. de Paris, 1907, Series 3, xxiv, 1169 and 1367; Compt. rend. Soc. de biol., 1907, lxiii, 672; Semaine méd. 1908, xxviii, 49; Allg. Wien. med. Ztg., 1908, liii, 462; Bull. et. mém. Soc. méd. d. Hôp. de Paris, 1908, Series 3, xxv, 411; 1908, Series 3, xxvi, 94; 1909, xxvii, 293.

10. Hutchison and Panton: Quart. Jour. Med., 1909, ii, 433.

11. Hawkins and Dudgeon: Quart. Jour. Med., 1909, ii, 165.

12. Widal: Bull. et mém. Soc. méd. d. hôp. de Paris, 1902, Series 3, xix, 984; 1907, Series 3, xxiv, 1127, 1354; 1909, Series 3, xxviii, 73; 1908, Series 3, xxv, 486; Gaz. d. hôp., 1907, lxxx, 1275; Presse méd., 1907, xv, 641; Compt. rend. Soc. de biol., 1907, lxiii, 346; 1908, lxiv, 496 and 655; 1909, lxvi, 927 and 950; Tribune med., 1907, xxxix, 711; Arch. d. mal. du coeur, 1908, I, 193.

duced by the liver cells as a result of attempts to change the increased amount of pigment arising from the destruction of the corpuscles. Whipple and Hooper[6] claim, however, that hemoglobin can be converted into bile pigments without participation of the liver. Roth[13] believes that hemolytic jaundice is a primary disease of the blood. Chauffard[14] thinks he has evidence pointing conclusively to an inherited taint, syphilis or tuberculosis, on which is added some abnormal action on the part of the spleen, as the factors responsible for congenital hemolytic jaundice.

It was thought that a complete metabolic study of this symptom-complex might throw some light on this disease. This was especially desirable on account of the fact that very little work has been done in this condition, from the metabolic standpoint. Tileston and Griffen studied the total nitrogen, urea-nitrogen, ammonia-nitrogen, creatin and creatinin in a case of chronic family jaundice for a period of three days. On a creatin- and purin-free diet, they found that the creatinin and urea values were normal, those for ammonia somewhat high. They found about 0.06 gm. of creatin in the urine per day and think the endogenous uric acid is distinctly increased. They report only one estimation of the uric acid in the complete study, however, so this result cannot be considered conclusive. They found, also, that tests for alimentary glycosuria and levulosuria were negative or inconclusive.

Minkowski[15] mentions that in a case of family hemolytic jaundice, Haal found an increased excretion of uric acid and a decided increase in the amount of iron in the urine.

Certain metabolic studies have been carried out in Banti's disease. It will be recalled that the name "Banti's disease" is reserved for those cases in which liver enlargement is secondary to the progressive enlargement of the spleen and associated with recurrent attacks of anemia and repeated hemorrhages from the stomach and bowels. As this disease is somewhat similar to the case described in this paper, it will be of value to review the metabolism studies carried out in Banti's disease. Umber[16] found a toxogenic decomposition of protein in a case of Banti's disease. He did not think it was due to the anemia present, but since the protein destruction disappeared after the removal of the spleen, he thought this destruction of the protein was due to a toxic agent produced in the spleen. This substance not only produced the anemia, but also affected the general metabolism of the organism.

In another case, with similar clinical symptoms, Umber found a retention of nitrogen and periodic variations in the excretion of the

13. Roth: Deutsch. Arch. f. klin. Med., 1912, cvi, 137.
14. Chauffard: Ann. d. méd., 1914, 1, 1.
15. Minkowski: Diseases of Digestive System, edited by Billings, p. 349.
16. Cited by Umber: Lehrbuch der Ernahrung, Berlin, 1909, p. 17.

urinary purin nitrogen. These values only slightly exceeded the upper limits for the normal excretion. The highest purin nitrogen excretion was 0.258 gm. Halpern,[17] in a case of splenic anemia, found that the average purin nitrogen excretion, on a purin-free diet, for a period of three days, was 0.253 gm.

II. CLINICAL DATA

Patient.—M. E. H., a girl aged 11, born in U. S. A., was first seen Nov. 26, 1913.

Family History.—Father, mother, one brother and two sisters are all living and well. No other member of the family is afflicted in the same manner as the patient. There is no history of consanguinity, alcoholism, lues, tuberculosis or cancer.

Previous History.—The patient had rubella, parotitis, varicella and pertussis. No history of scarlet fever or diphtheria. Tonsillitis several years ago. No pleurisy or pneumonia. Slight attack of bronchitis this winter. Six years ago had an acute illness, with temperature 106 for a few hours. On the second day the symptoms disappeared and in one week the patient was well. At this time the enlargement of the spleen was first noted. Patient has never been strong; was treated six years ago with x-rays for a period of two weeks.

Present Illness.—Child has always had waxen color with a lemon tint. There has been no pruritus, no epistaxis, no dyspnea and no gastric symptoms. Bowels are regular, no diarrhea. Stools have been normal in color, but for two years after birth they were very green. The appetite is variable. No nausea or vomiting. Since her illness, six years ago, the spleen has been growing larger and the size is variable. The jaundice has been present since three or four weeks after birth.

Chief Complaint.—Enlargement of the spleen and persistent jaundice.

Examination.—General: The patient is underdeveloped and poorly nourished, weighing 63½ pounds. The skin is of a lemon yellow color, and the mucous membranes are pale. There are no eruptions. The cervical glands of the left side are slightly enlarged; submaxillary glands are enlarged; the axillary and epitrochlears are not palpable. Temperature 98, pulse 112.

Head: The nose, mouth and pharynx are normal. Tonsils large and ragged. The cranial nerves are normal, the teeth good, the thyroid not enlarged.

Eyes: The conjunctivae have a lemon yellow color. The pupils react moderately slowly to light and accommodation. Nystagmus to the left.

Chest: No deformities, no enlargement of thymus.

Lungs: Clear throughout.

Heart: Overacting. A blowing systolic murmur at the apex, over the pulmonary area, and transmitted to the left. The pulmonic second sound is accentuated.

Abdomen: Moderately distended and tympanitic. No abnormal masses, no areas of tenderness nor rigidity.

Liver: Extends from fifth space. The edge is palpalble one-half inch below the costal border in the mammary line. The edge is firm and normal in outline.

Spleen: Extends forward to within one-half inch of midline and downward to the lower border of the umbilicus.

Kidneys: Not palpable.

Appendix and Colon: Negative.

Extremities: No edema or tenderness over large bones. The knee-jerks are normal.

17. Von Noorden: Metabolism and Practical Medicine, ii, 368.

Urine: Deep amber, clear, acid, specific gravity 1.021, no protein, no sugar, no bile, indican very slight. Microscopically contains a few squamous epithelial cells and a few leukocytes and erythrocytes.

Blood-Count: December 6, red blood-cells, 3,560,000; hemoglobin, 48 per cent. (Sahli N. S.); white blood-cells, 11,200; polynuclears, 78 per cent.; small lymphocytes, 14 per cent.; large lymphocytes, 3 per cent.; transitionals, 0.5 per cent.; eosinophils, 4.0 per cent.; neutrophils, 0.5 per cent. The red corpuscles show a definite variation in size, poikilocytosis present in mild degree. The red corpuscles stain uniformly well. No abnormal granulations present. One nucleated red corpuscle seen in making differential count of 200 cells. Blood platelets are present but relatively scarce. Blood-count: Feb. 14, 1914, hemoglobin, 55 Sahli (N. S.), red blood-cells, 3,740,000; white blood-cells, 12,600; polynuclears, 65 per cent.; small lymphocytes, 24 per cent.; large lymphocytes, 6 per cent.; transitionals, 2 per cent.; eosinophils, 3 per cent. Poikilocytosis, anisocytosis, variation in staining. Moderate number megalocytes, many microcytes, no nucleated reds.

Stools: Negative for blood, parasites or ova.

Wassermann reaction is negative.

III. HEMOLYSIS TESTS OF PATIENT'S BLOOD

The work of Vaquez and Ribierre has demonstrated that in conditions of obstructive jaundice, the erythrocytes have an increased resistance to hemolysis by hypotonic salt solution. Chauffard and others,[18] in contrast to these results, found that the corpuscles in three cases of chronic acholuric icterus presented a greatly diminished resistance. Chauffard found that in normal individuals hemolysis started on addition of 0.44 per cent. sodium chlorid solution and was complete at 0.36 per cent.

TABLE 1.—HEMOLYSIS TESTS OF PATIENT'S BLOOD, DEC. 14, 1913*

	Strength of NaCl Solution in Per Cent.											
	0.375	0.4	0.425	0.45	0.5	0.525	0.55	0.575	0.6	0.625	0.65	0.9
Patient's blood	+++++	+++++	+++++	++++	++++	++++	+++	+++	+++	++	+	0
Control normal	+	++	0	0	0	0	0	0	0	0	0	0

* Washed cells used. In this table +++++ equals complete hemolysis; ++++ equals moderate hemolysis; +++ equals slight hemolysis; ++ equals very slight hemolysis; + equals trace of hemolysis; 0 equals no trace of hemolysis.

In testing the osmotic resistance of the red cells of this patient, the same technic was used as that described by Richards and Johnson.[5] Table 1 contains the results obtained in this study, showing that the red cells of this patient had a lessened resistance toward salt solution.

18. Chauffard: Compt. rend. Soc. de biol., 1902, liv, 1074. Von Stejskal: Wien. klin. Wchnschr., 1909, xxii, 1701. Butler: Quart. Jour. Med., 1913, vi, 145. Massaglia and Tarabina: Gazz. d. osp. e. de clin., 1908, xxix, 778. Pel: Deutsch. Arch. f. klin. Med., 1912, cvi, 239. Maliwa: Deutsch. med. Wchnschr., 1913, xxxix, 154. Roth: Deutsch. Arch. f. klin. Med., 1912, cvi, 137. Cade: Bull. et mém. Soc. méd. d. hôp. de Paris, 1908, xxv, 421.

IV. METABOLIC DATA

The patient was placed on Folin's[19] diet in quantities of about one-half the original amounts. It consisted of:

Whole milk, 300 c.c.; cream, 150 c.c.; malted milk, 100 gm.; sugar, 10 gm.; salt, 4 gm.; butter, 5 gm.; eggs (minus shell), about 240 gm.; water, 1,000 c.c.

This diet contains approximately 60 gm. of protein, 75 gm. of fat and 112 gm. of carbohydrate, yielding 1,395 calories or about 50 calories per kilogram body weight of the patient.

Two ounces of the above-described diet was taken out daily and the following constituents estimated: total nitrogen, phosphorus, sulphur, iron, calcium and magnesium. The fat was estimated in the five-day sample, preserving 5 c.c. of each day's mixture by means of two drops of liquor formaldehydi.

TABLE 2.—THE NITROGEN METABOLISM—

Date 1913	Vol.	Acidity in Amt. of N/10 NaOH necessary to neutralize total urine	Total Nitrogen	Urea Nitrogen		Ammonia Nitrogen		Creatinin †		
			gm.	gm.	% of total N.	gm.	% of total N.	gm.	Nitrogen	% of total N.
12/10	960	186.2	7.02	6.01	85.6	0.32	4.5	0.48	0.174	2.50
12/11	1100	294.8	8.32	7.06	84.8	0.34	4.0	0.45	0.163	1.96
12/12	975	227.6	8.35	7.04	84.3	0.35	4.1	0.36	0.131	1.57
12/13	1175	305.5	8.36	7.12	85.2	0.38	4.5	0.44	0.160	1.91
12/14	880	206.2	8.40	7.20	85.7	0.36	4.3	0.44	0.160	1.90
12/15	1050	302.4	8.10	7.18	88.6	0.32	4.0	0.42	0.152	1.88

† Creatin was not present in the urine at any time.

A. The Method Used in Urine Analysis.—The nitrogen was estimated according to Kjeldahl, the total sulphur by Benedict's[20] method, total and ethereal sulphates by Folin's[21] method, the inorganic sulphates computed by subtracting the ethereal sulphates from the total sulphates and the neutral sulphur by subtracting the total sulphate sulphur from the total sulphur. The urea was estimated by Benedict's[22] method. The ammonia by Folin's method,[23] the total phosphorus by the Neumann method,[24] weighing the phosphorus as magnesium pyrophosphate. The iron was estimated by Neumann's[25] method, the total phosphates and earthy phosphates by titration with uranium acetate

19. Folin, O.: Am. Jour. Physiol., 1905, xiii, 45.
20. Benedict: Jour. Biol. Chem., 1909, vi, 363.
21. Folin: Am. Jour. Physiol., 1905, xiii, li; Jour. Biol. Chem., 1906, 1, 131.
22. Benedict: Jour. Biol. Chem., 1911, viii, 405.
23. Folin: Ztschr. f. physiol. Chem., 1902, xxxvii, 161; Am. Jour. Phys., 1903, viii, 330.
24. Neumann: Ztschr. f. physiol. Chem., 1902-03, xxxvii, 129; 1904-05, xliii, 35.
25. Neumann: Ztschr. f. physiol. Chem., 1903, xxxvii, 114.

solution; creatinin and creatin by Folin's methods[19]; uric acid by Folin's[26] method; calcium and magnesium by McCrudden's[27] method; amino-acid by Benedict and Murlin's method,[28] and total acidity by Folin's method.[29]

B. Methods Used in the Analysis of the Food.—The nitrogen by Kjeldahl method; total sulphur by Wolff and Osterberg[30] modification of Benedict's method; calcium and magnesium by McCrudden's method, after ashing and extracting the ash with hydrochloric acid; the phosphorus and iron by Neumann's method. The fat was estimated in a five-day period by Soxhlet extraction.

C. Methods Used in Analysis of Feces.—The feces were marked off by means of carmin into a period of five days. The nitrogen was estimated by Kjeldahl method; sulphur by oxidizing with fuming acid,

—AND URINARY NITROGEN PARTITION *

Uric Acid			Amino-Acid Nitrogen		Undetermined Nitrogen		Feces Total Nitrogen		Nitrogen		
gm.	Nitrogen	% of total N.	gm.	% of total N.	gm.	% of total N.	gm.	% of total N.	Intake gm.	Output gm.	Balance gm.
0.42	0.143	2.04	0.08	1.2	0.29	4.1	0.77	10.9	8.04	7.79	+ 0.25
0.35	0.120	1.44	0.18	2.2	0.46	5.5	0.77	9.3	8.15	9.09	— 0.94
0.41	0.137	1.64	0.15	1.8	0.54	6.5	0.77	9.2	8.25	9.12	— 0.87
0.33	0.110	1.22	0.20	2.4	0.39	4.7	0.77	9.2	8.05	9.13	— 1.08
0.49	0.143	1.70	0.17	2.0	0.37	4.4	0.77	9.2	8.25	9.17	— 0.92
0.41	0.137	1.70	0.14	1.7	0.17	2.1	0.77	9.5	8.37	8.87	— 0.50

† Average creatinin coefficient equals 5.9 mg. of creatinin-nitrogen per kilogram of body weight.

followed by Benedict's method; phosphorus and iron by the Neumann method; calcium and magnesium by the same method as used for the food; the fat by Soxhlet extraction. Tables 2, 3 and 4 contain the results obtained in this study.

Discussion of Table 2.—In the period of five days, there was a loss of 4.06 gm. of nitrogen, which might be considered as evidence pointing toward a toxogenic destruction of protein in this patient. The absorption of nitrogen is normal. The urinary nitrogen partition is normal with the exception of the uric acid, which shows a decided increase. This increase might be due to the fact that owing to the hemolysis of the erythrocytes, nucleoprotein is liberated from which the uric acid is formed and thereby an increased urinary excretion of endogenous uric acid is produced. This result speaks in favor of an increased destruction of the red cells as being a part of the condition.

26. Folin: Ztschr. f. physiol. Chem., 1901, xxxii, 552.
27. McCrudden: Jour. Biol. Chem., 1911, x, 187.
28. Benedick and Murlin: Jour. Biol. Chem., 1913, xvi, 385.
29. Folin: Am. Jour. Physiol., 1903, viii, 265.
30. Wolf and Osterberg: Biochem. Ztschr., 1910, xxix, 429.

TABLE 3.—The Sulphur Metabolism and Urinary Sulphur Partition

Date 1913	Vol. c.c.	Total S. gm.	Total sulphate S.		Ethereal sulphate S.		Inorganic sulphate sulphur		Neutral sulphur		Feces S.	Sulphur		
			gm.	% of total S.	gm.	% of total S.	gm.	% of total S.	gm.	% of total S.	gm.	Intake gm.	Output gm.	Balance gm.
12/10	950	0.68	0.58	85.3	0.18	26.5	0.40	58.8	0.10	14.7	0.156	0.50	0.836	— 0.336
12/11	1100	0.79	0.70	88.6	0.07	8.8	0.63	79.8	0.09	11.4	0.156	0.41	0.790	— 0.38
12/12	975	0.74	0.64	86.5	0.14	18.9	0.50	67.6	0.10	13.5	0.156	0.54	0.896	— 0.356
12/13	1175	0.73	0.61	83.5	0.13	17.8	0.48	65.7	0.12	16.4	0.156	0.46	0.886	— 0.426
12/14	880	0.75	0.65	86.6	0.35	46.7	0.30	39.9	0.10	13.3	0.156	0.52	0.906	— 0.386

Discussion of Table 3.—The urinary sulphur partition is normal in character, with the exception of a marked increase in the excretion of the ethereal sulphates on the first and last days of the metabolism experiment. This is due, no doubt, to an increased intestinal putrefac-

TABLE 4.—The Mineral Metabolism—

Date	Urine								Feces	
	CaO gm.	MgO gm.	Fe gm.	Total phosphate P. gm.	Total phosphate P. % of total P.	Earthy phosphate P. gm.	Earthy phosphate P. % of total P.	Total P. gm.	CaO gm.	MgO gm.
12/10	0.304	0.292	0.00877	0.62	91.2	0.17	24.7	0.68	0.76	0.26
12/11	0.428	0.264	0.00872	0.75	96.1	0.20	25.6	0.78	0.76	0.26
12/13	0.434	0.266	0.00874	0.66	94.3	0.12	17.1	0.70	0.76	0.26
12/14	0.640	0.254	0.00871	0.66	88.0	0.34	45.3	0.75	0.76	0.26
12/15	0.256	0.206	0.00881	0.60	92.3	0.24	36.9	0.65	0.76	0.26

tion. In the five days the patient lost 1.88 gm. of sulphur. This would be expected on account of the fact that our patient was also losing nitrogen.

Discussion of Table 4.—In the five-day metabolism experiment the patient lost 0.482 gm. of calcium oxid and 0.924 gm. of magnesium oxid. There was a phosphorus retention of 0.07 gm., and the amounts of total phosphates and earthy phosphates may be considered normal. There was also an iron loss of 0.1199 gm. The metabolism of iron in the case studied is of special interest on account of the relation of the spleen to the disintegration of red cells, and also on account of the increased hemolysis present in this disease.[31]

To interpret our results, it will be necessary to review briefly some of the more important papers that have appeared on the metabolism of iron. Lehmann, Müller, Munk, Senator and Zuntz[32] in 1893 published an extended study of the metabolism of the professional fasters,

31. For discussion of iron in food and its function in nutrition see Sherman: Bulletin 185, U. S. Dept. Agric., Off. Exper. Sta., 1907.

32. Lehmann, Müller, Munk, Senator and Zuntz: Arch. Path. Anat. u. Phys. (Virchow), 1893, p. 131, Supp.

Cetti and Breithaupt. During a ten-day fast, Cetti lost 7.3 mg. iron in the feces per day. Breithaupt fasted six days and lost 7.7 mg. iron in the feces per day. Stockman and Grieg[33] studied three normal cases and one chlorotic as regards the iron metabolism. Their results may be seen in Table 5.

TABLE 5.—Iron Metabolism in Cases of Stockman and Grieg

Experiment No.	Subject	Age	Iron in Food mg.	Iron in Feces mg.	Iron in Urine mg.	Balance mg.
1	man	20	6.2	5.07	1.27	— 0.14
2	man	35	6.2	8.10	1.23	— 3.13
3	man	20	5.6	10.87	0.67	— 5.94

—(Calcium, Magnesium, Phosphorus and Iron)

Feces		Balance							
		Calcium oxid		Magnesium oxid		Phosphorus		Iron	
Phosphorus gm.	Iron gm.	Intake gm.	Balance gm.	Intake gm.	Balance gm.	Intake gm.	Balance gm.	Intake gm.	Balance gm.
0.48	0.02396	0.93	— 0.134	0.32	— 0.292	1.2	+ 0.04	0.0084	— 0.0234
0.48	0.02396	0.82	— 0.256	0.38	— 0.144	1.3	+ 0.04	0.0096	— 0.0231
0.48	0.02396	1.04	— 0.154	0.36	— 0.166	1.15	— 0.05	0.0088	— 0.0239
0.48	0.02396	1.20	— 0.20	0.34	— 0.174	1.17	— 0.06	0.0084	— 0.0244
0.48	0.02396	1.28	+ 0.262	0.32	— 0.148	1.21	+ 0.08	0.0086	— 0.0242

Von Wendt[34] has reported six metabolism experiments, covering thirty-five days, in which the income and outgo of iron was determined. He estimates that an average mixed diet will contain from 20 to 30 mg. of iron. His results are presented in Table 6.

TABLE 6.—Iron Metabolism in von Wendt's Cases

Experiment No.	Iron in Food gm.	Iron in Feces gm.	Iron in Urine gm.	Balance gm.
1	0.100	0.008	0.001	+ 0.001
2	0.006	0.010	0.001	— 0.005
3	0.016	0.013	0.001	+ 0.002
4	0.008	0.008	0.001	— 0.001
5	0.017	0.041	0.001	— 0.025
6 (a)	0.016	0.015	0.001	0
6 (b)	0.007	0.015	0.001	— 0.009

33. Stockman and Greig: Jour. Physiol., 1897, xxi, 55.
34. Von Wendt: Skand. Arch. Physiol., 1905, xvii, 211.

Sherman's results on the metabolism of iron are given in Table 7.

In closing, Sherman claims that the amount of iron metabolized in the body so as to be eliminated, in health is small, in fasting experiments 7 or 8 mg.; in metabolism experiments with restricted diets from 5.5 to 12.5 mg. per day, and that the amount of food-iron required for the maintenance of the equilibrium in healthy men lies between 6 and 12 mg. per day.

TABLE 7.—IRON METABOLISM

Experiment No.	Iron in Food daily	Iron in Feces daily	Iron in Urine daily	Balance daily
1	0.0057	0.0053	0.0002	+ 0.0002
2	0.0065	0.0085	0.0002	— 0.0022
3	0.0071	0.0124	0.0002	— 0.0055

At present, since the work of Neumann[35] and of Neumann and Mayer,[36] about 1 mg. of iron, in the urine, for a period of twenty-four hours, is considered the normal output. In diseases of the blood, the following results have been obtained as regards the urinary excretion of iron. Zander[37] claims to have found a decided decrease in the urinary iron in chloranemia. Quincke,[37] however, showed that the excretion of iron was increased in the beginning of the disease, while later there was a lessened excretion. Lehmann[37] also found an increased excretion. Hunter[38] and Jolles and Winkler[39] have reported marked reductions in the urinary excretion of iron in chloranemia. Hunter[40] found a marked increased in the excretion of iron in pernicious anemia, at one time 32.26 mg. were excreted daily in the urine. Damaskin,[31] in pernicious anemia, reported an increased excretion, while Hopkins[41] found the excretion varied from traces to 8.3 mg. per day. In leukemia, an increased excretion of iron has also been found.[42] On comparing the results obtained as regards the iron metabolism in the study of this case of hemolytic jaundice with splenomegaly, with the results summarized above, it can readily be noted that there is a marked increase in the excretion of urinary and fecal iron, as would be

35. Neumann: Ztschr. f. physiol. Chem., 1903, xxxvii, 114.
36. Neumann and Mayer: Ztschr. f. physiol. Chem., 1903, xxxvii, 2 and 143.
37. Cited from Kennerknecht: Virchow's Arch. f. path. Anat., 1911, ccv, 89 (contains the literature).
38. Hunter: Brit. Med. Jour., 1890, ii, 1.
39. Jolles and Winkler: Arch. f. exper. Path. u. Pharm., 1900, xliv, 464.
40. Hunter: Practitioner, 1889, xliii, 161, 321, 401.
41. Hopkins: Guys Hosp. Reports, 1894, vii, 373.
42. Hoffmann: Zeit. f. anal. Chem., 1901, lxxiv, 40.

expected in a disease in which we have a hemolytic jaundice combined with an increased fragility of the red cells, and that the increased excretion is due to the liberation of the iron from the broken-down red cell.

TABLE 8.—The Fat Metabolism *

	Date 12/10-12/14
Fat (gm.) in feces	18.0
Per cent. of fat in dried stool	26.2
Per cent. of fat intake	9.1
Per cent. of fat absorbed	90.9
Intake of fat (gm.)	165
Per cent. of neutral fat in stool fat	37
Per cent. of fatty acid in stool fat	27
Per cent. of soaps in stool fat	36

* Cholesterol not included.

Discussion of Table 8.—The fat metabolism is normal in character, with an absorption of 90.9 per cent. of the ingested fat. The amount of neutral fat, fatty acids and soap in the stool is normal, thereby excluding this as the cause for the loss of the calcium and magnesium.

TABLE 9.—Tests of Urine and Feces for Urobilin, Urobilinogen, Bilirubin and Hemoglobin * *

Date	Urine				Feces		
	Urobilin*	Urobilinogen*	Bilirubin†	Hemoglobin‡	Urobilin‡	Bilirubin‡	Hemoglobin§
12/ 6	0	+	0	0	+	0	0
12/ 8	+	+	0	0	+	0	0
12/10	0	+	0	0	+	0	0
12/11	+	+	0	0	+	0	0
12/12	0	0	0	0	+	0	0
12/13	+	+	0	0	+	0	0
12/14	+	+	0	0	+	0	0
12/15	+	+	0	0	+	0	0
12/16	+	+	0	0	+	0	0

* Dimethylamidobenzaldehyd and spectroscopic tests used.
† Nakayamas and Gmelin's tests used.
‡ Schmidt's test used.
§ Spectroscopic and benzidene tests.
** In this table the sign + stands for present and 0 for absent.

Discussion of Table 9.—Although urobilin is present in the urine normally, in small quantities, its presence cannot be detected by the tests used. A positive reaction with Ehrlich aldehyd reagent or with Schlesinger's zinc acetate test usually means that there has been either an abnormal destruction of red blood-cells or an insufficiency of the liver to perform its normal function.[43] We think, therefore, that the marked reaction for urobilin in the feces and urine of our case may be taken as an indication of the increased hemolysis present in this condition. In the case studied by McPhedran and Orr,[44] they found six times as much urobilin in the feces as in the stools of a normal control. Moller[45] found also that the total urobilin excretion in the urine and feces is greatly increased (400 mg. in twenty-four hours). It may also be noted that blood and bile pigments were absent from the urine and feces.

V. SUMMARY

1. A case of congenital hemolytic jaundice with splenomegaly and increased fragility of the red cells is described together with a metabolism experiment.

2. In a metabolism experiment of five days, there was a loss of 4.06 gm. of nitrogen, while the urinary nitrogen partition is normal in character with the exception of the uric acid nitrogen, which is increased. The absorption of nitrogen was normal.

3. The urinary sulphur partition is normal in character with occasional increased excretions of ethereal sulphates. In the five days there was a loss of 1.88 gm. of sulphur.

4. In the five days there was a loss of 0.482 gm. of calcium oxid and 0.924 gm. of magnesium oxid. There was a phosphorus retention of 0.07 gm., while the amounts of earthy phosphates and total phosphates may be considered normal.

5. There was a loss of 0.1199 gm. of iron in the five days, with marked increased amounts of iron excreted in the urine and feces.

6. The fat metabolism was normal, with an absorption of about 91 per cent. of the ingested fat. The amounts of neutral fat, fatty acids and soaps in the stool were normal.

7. Urobilin and urobilinogen were present in the urine and feces. Bilirubin and hemoglobin were absent from the urine and feces.

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43. For a complete discussion of urobilin see Wilbur and Addis: Urobilin: Its Clinical Significance, THE ARCHIVES INT. MED., 1914, xiii, 235.
44. McPhedran and Orr: Canad. Med. Jour. Assn., 1913, iii, 14.
45. Moller: Berl. klin. Wchnschr., 1908, xlv, 1639.

FUNCTIONAL CHANGES IN EXPERIMENTAL HYDRONEPHROSIS*

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The effects of back-pressure on the kidney have been studied by a number of investigators in the clinical, physiological and pathological fields. The records of experimental and clinical cases show that with partial or complete occlusion of the ureter hydronephrosis almost invariably results. Instances in which atrophy has occurred have been reported, but a careful study of the records reveals but few in which there was a true, primary atrophy—that is, one that was not preceded by a temporary hydronephrosis. A thorough review of the literature on this point has recently been presented by Scott.[1] Kawasoye,[2] in a publication that appeared at about the same time, discusses at length the difficulty of producing complete atresia of the ureter. His own method consisted in tightly knotting the ureter and ligating the free end. In ten rabbits so treated, the histological evidences of hydronephrosis were found in every instance, the duration varying from two to seventy days.

As regards the physiological effects of back-pressure on the kidneys, the work of previous investigators is here reviewed, because the experimental studies presented in this article are essentially functional. Their methods of procedure can be grouped into two classes, fundamentally different one from the other. In the first group the methods, in general, consisted in establishing a constant pressure in one ureter and comparing the secretory ability of this kidney with that on the opposite side. The determinations were not preceded by any prolonged back-pressure, and consequently the results represent simply the ability of a normal kidney to secrete against an increased pressure. In the second group one ureter was ligated, and after a varying length of time the obstruction was released and the functional capacity of the two sides compared. The latter methods give rise to conditions that approach more nearly a true pathological picture, for

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1. Scott, G. D.: Experimental Hydronephrosis, Surg., Gynec. and Obst., 1912, xv, 296.

2. Kawasoye, M.: Experimentelle Studien zum künstlichen Ureterverschluss, Ztschr. f. Gynäk., Urol., 1911-1912, iii, 172.

the results represent the functional derangement following the damage to the kidney by prolonged intrapelvic pressure.

First Group.—Hermann,[3] working in Ludwig's laboratory, in 1859, found that an intra-ureteral pressure of less than 50 mm. of mercury resulted in a diminution in the flow of urine and in the secretion of urinary solids. A pressure above 50 mm. of mercury caused a complete suppression. Lépine and Porteret,[4] experimenting on dogs, found that with intra-ureteral pressures of from 20 to 45 cm. of water, the secretion of water and chlorids was diminished. They note the interesting fact that when the pressure was low the diminution in the amount of urea was relatively more marked than that of the water and chlorids, while with higher pressures the water and chlorids were more diminished than the urea. Lindemann,[5] working on dogs, found that with a pressure in one ureter of from 10 to 43 cm. of water, the amount of urine and urea was lessened, as compared with the other side, while the sodium chlorid remained unchanged. With a pressure below 50 mm. of mercury the blood-flow through the kidney was unaffected, but with one of from 50 to 210 mm. the flow was retarded. Schwartz[6] reported in 1902 that the kidney (in dogs) under a back-pressure of from 10 to 25 cm. of water secreted more urine, but of a lower specific gravity; although the concentration of urea, nitrogen and sodium chlorid was less, the absolute output of these substances was greater on account of the increased volume of urine. After the injection of phloridzin, reducing bodies were more marked in the urine from the pressure side. Methylene blue appeared simultaneously from both ureters. Under the influence of diuretics, sodium chlorid or sodium iodid, the amount of urine which flowed from the affected side was double that from the other, the percentage of chlorids and iodids less, while the absolute amount was greater. If the pressure was maintained beyond the usual time (from seventy-five to 150 minutes) or if it was raised, diuresis stopped. Working on rabbits he found that a pressure of from 2 to 3 cm. of water stopped the secretion. Cushny[7] worked on rabbits and

3. Hermann, M., quoted from Cohnheim: Lectures on General Pathology, translation by A. B. McKee, London, 1890, p. 1223; Back Pressure on the Ureter and Its Effects on Urinary Flow, Sitzungsberichte der Wiener Akademie, xxxvi, 1859.

4. Lépine and Porteret: Sur la composition de l'urine sécrétée pendant la durée d'une contre pression exercée sur les voies urinaires, Compt. rend. Acad. d. Sc., 1888, cvii, 74.

5. Lindemann, W.: Ueber die Wirkung der Gegenrückerhöhung auf die Harnsecretion, Z. path. Anat. u. allg. Path., 1897, xxi, 500.

6. Schwartz, Leo: Ueber Harnveränderung nach Ureterbelastung, Zentralbl. f. Physiol., 1902, xvi, 281.

7. Cushny, A. R.: On Saline Diuresis, Jour. Physiol., 1902, xxviii, 431.

found that with a pressure of 30 mm. of mercury, after the intravenous injection of sodium chlorid and sodium sulphate, the volume of urine and the concentration of the chlorids and sulphates was less from the affected side. Later the same investigator reported[8] a repetition of these experiments on dogs, with the same findings. Filehne and Ruschhaupt[9] found that in rabbits a pressure in one ureter of from 7 to 27 cm. of water caused uniformly a diminution in the amount of urine from that side, diuretics having been injected. On release of pressure there followed a greater urinary flow from the affected side than from the normal one. Brodie and Cullis,[10] working on decerebrated dogs, found that a back-pressure of from 10 to 20 cm. of water in one ureter caused an increased flow of urine and an increased elimination of sulphates during the diuresis caused by the injection of sodium sulphate. This effect is most marked at 10 cm. of water, and they placed the limits of increased secretion at from 10 to 20 cm. They confirm the observation of Schwartz that the excretion of reducing bodies, following the injection of phloridzin, is greater from the pressure side.

Second Group.—Heidenhain[11] tied one ureter (in rabbits), and after twenty-four hours injected indigocarmin. As soon as the dye appeared in the urine from the normal side, the animal was killed and the deposition of the indigocarmin in the two kidneys was studied grossly and microscopically. He notes that in all cases the ureter was distended above the ligature and the kidney on that side was edematous. The blue dye was evident, grossly, in both kidneys but was distinctly less in the affected one. Microscopic examination showed that while clumps of the carmin were lying in the lumen of the tubules, yet the blue granules were not present in the tubular cells as in the normal kidney. Lindemann[12] ligated the ureter on one side, and after an hour and a half studied the excretion of indigocarmin from the two kidneys. He found that there was a diminution in the amount of the dye excreted by the affected side. Pfaundler[13] tied the ureter

8. Cushny, A. R.: Acid Secretion by the Kidney, Jour. Physiol., 1904, xxxi, 188.

9. Filehne and Ruschhaupt: Die Diurese bei Abflusserschwerung, Arch. f. Physiol., 1903, xcv, 409.

10. Brodie, T. G., and Cullis, W. C.: On the Secretion of Urine, Jour. Physiol., 1906, xxxiv, 224.

11. Heidenhain, R.: Versuche üeber den Vorgang der Harnabsonderung, Arch. f. Physiol., 1874, ix, 10.

12. Lindemann, W.: Ueber Veränderungen der Nieren infolge von Ureterunterbindung, Ztschr. f. klin. Med., 1898, xxxiv, 299.

13. Pfaundler: Ueber die durch Staung im Ureter zu Stande kommende Veränderung der Harnsecretion, Beitr. z. Chem. Phys. u. Path. (Hofmeister's), 1902, No. 2, p. 330.

on one side (in dogs), and after varying intervals of time (from fifteen minutes to six hours), collected the fluid which had accumulated behind the ligature and compared it with that secreted by the other kidney during the same period. He found that the volume of urine was greater, but that the concentration of urea and sodium chlorid was less. Bainbridge[14] ligated one ureter (in cats) and after varying intervals of time anesthetized the animal, measured the pressure in the ureter and tested the fluid that had accumulated back of the obstruction. He then emptied the pelvis, effected diuresis by the injection of salt, and collected the urine from the sound and the hydronephrotic kidney. He found that the secretory power of the affected kidney, as evidenced by the amount of water and solids collected, steadily diminished from day to day but was not entirely lost at the end of two months. If tested within a few days the damaged kidney sometimes secreted more water, but the nitrogen total was always low. The ability to excrete acids, also, was impaired. Kawasoye[2] tied off one ureter in each of nine rabbits, killing them at intervals varying from a few hours to a month; in each case indigocarmin was injected twenty minutes before death. Histological examination showed that the dye was present in the tubular epithelial cells in decreasing amounts up to twenty-four hours, and after forty-eight hours none was seen. In another series of seven rabbits the obstruction was relieved at varying intervals of time, and it was found that complete restoration of functional ability, as shown by indigocarmin as a test, took place after four days, incomplete restoration after from seven to fourteen days, and after twenty-one days no dye at all was secreted. Steyrer[15] reports two clinical cases in which a partial atresia of one ureter was caused by a unilateral ureterovaginal fistula. The urine was collected from the two sides simultaneously and studied. He observed that in both cases the urine from the affected side was increased in amount but of a lower specific gravity and molecular concentration than that from the normal side.

As a result of the work of these investigators it is quite clear that increased back-pressure on the kidney will cause definite functional changes. The amount of urine secreted apparently varies with the degree of intra-ureteral pressure, there being, with low pressures, an increased flow, while with higher pressures, the flow is diminished. With but one exception (Brodie and Cullis) there is reported a decrease in the concentration of solid constituents. The excretion of indigocarmin is materially reduced, as agreed by all.

14. Bainbridge, F. A.: The Effects of Ligature of One Ureter, Jour. Path. and Bacteriol., 1906, xi, 421.

15. Steyrer, Anton: Ueber Osmotische Analyse des Harns, Beitr. z. chem. Phys. u. Path. Hofmeister's, 1902, No. 2, 312.

The effects produced by back-pressure, extending over a longer period of time than the foregoing experiments—conditions more nearly approaching that met clinically, have not been previously undertaken. For this reason we present a study of the functional changes that occur from day to day in an animal when the only deviation from normal is an increased intra-ureteral pressure.

METHOD OF PROCEDURE

In order to study the effects of increased back-pressure on the kidney in the living animal, over an extended period of time, three procedures are open: first, to obstruct the urethra; second, to produce a partial occlusion of both ureters, or, third, to produce an obstruction in one ureter, with removal of the kidney on the other side. The latter method was considered to be the most reliable, in that evidences of functional changes could be definitely attributed to the involvement of the one kidney. Before adopting it, however, a unilateral nephrectomy was performed in two dogs and the functional tests carried out several times during the succeeding two weeks. No change from the normal was found.

Several devices for producing a partial obstruction of the ureter were then tried. Rigid bands, sections of silk urethral catheters, were at first used, being placed about the ureter and held in position by silk sutures. This method proved to be unsatisfactory, in that it entailed stripping a short length of the ureter, resulting in a localized edema and marked narrowing.

Elastic bands were next employed, the use of which was suggested by Scott's work,[1] and a preliminary trial on the ureter of a dog which had just been killed, gave promise of success. The kidneys, ureters and bladder were dissected free, placed in their normal relations in warm, phyiological saline solution, and the experiment conducted as follows: A rubber band, 1.5 mm. in width and 1 mm. in thickness, was placed about the ureter, from 3 to 4 cm. above its entrance into the bladder, the ends of the elastic being held together by silk suture. The bladder was laid open so that the ureteral orifice was plainly visible at the trigone. A cannula was inserted into the ureter above the obstruction. To this cannula was attached a water manometer, the fluid, normal saline, being colored by an indicator, and the pressure determined at which the fluid escaped past the obstruction. When the elastic band was tightly fixed about the ureter, but without tension, it was found that a water pressure of 100 cm. was necessary before the fluid passed the obstruction; whereas when the elastic band was more loosely placed—that is, when a definite clear space could be seen between the ureteral wall and the point where the silk ligature held the

ends of the rubber band — the ureter became permeable at a pressure of from 20 to 30 cm. of water. In light of the results of previous investigators we considered this to be the pressure most likely to produce the desired effects.

This method was then applied to the living animal, as follows:

Dog 15.—A small, black, male dog, weighing 5.5 kg., was operated on in the following manner: The abdominal wall was shaved and the skin cleaned in the usual way. Rigid, aseptic surgical technic was employed throughout. Under ether anesthesia the abdomen was opened in the median line, the intestine packed off, the left kidney decapsulated, and the stalk containing the renal artery, vein and ureter was ligated and sectioned. Following left nephrectomy, the right ureter was palpated just above its entrance into the bladder wall and a rubber band was passed around it and tied as described above.[16] The abdominal wall was closed in three layers with continuous silk sutures. As it was impossible to catheterize such a small male animal no functional studies were performed in the next week, the urine only being examined in the routine manner for albumin and casts. The animal passed at least an average daily amount of urine and appeared to be in good health. The full allowance of meat and water was taken and there was no loss of weight. One week after the operation the dog was killed, and a definite enlargement of the right ureter above the band, with a moderate hydronephrosis and enlargement of the right kidney was found. The capsular veins were enlarged and very prominent. Otherwise the necropsy revealed nothing abnormal, there being no evidence of infection in the urinary tract or elsewhere in the body.

The pressure of water necessary to overcome the obstruction was then determined in the manner previously described. This pressure was found to be 30 cm. of water. Histologically, the right kidney showed marked and uniform dilatation of the tubules of the pyramids. The convoluted tubules were but slightly dilated and their epithelium was columnar. Few casts were seen. The glomeruli showed no change. The walls of the larger blood-vessels were thickened.

The method proving satisfactory, we proceeded to apply it to female dogs and study the renal function before and after operation. In only one of the seven submitted to this procedure did the method fail to produce the desired effect. In this instance, Dog 13, the elastic band was placed too tightly about the ureter, and although the animal passed between 100 and 200 c.c. of urine in forty-eight hours, anuria then developed, followed by the typical course of complete renal insufficiency as observed in dogs. The pressure necessary to overcome the obstruction, determined at necropsy, amounted to 70 cm. of water, much above that determined at the necropsies of the remaining six animals. There was moderate distention of the ureter above the obstruction with definite dilatation of the pelvis of the kidney. The whole organ was larger than the one previously removed from the other side. The capsular veins were engorged.

Histological Examination: The glomerular capsules were dilated and the tufts did not fill the capsular space. The tubules in general were slightly dilated, although this was not so marked as the glomerular change. The tubules were filled with amorphous, pink material which suggested forming casts. The epithelium of the tubules was swollen and watery, the differentiation between the epithelium and masses of exudate being very poor. The interstitial tissue was less conspicuous than normal.

16. More accurate methods of estimating this pressure at operation are being considered.

METHODS USED IN THE FUNCTIONAL STUDIES

The dogs were kept in metabolism cages, given a constant diet, 200 gm. of ground beef, and allowed to drink as much water as they desired. The beef was frequently analyzed for the total nitrogen content. It is to be emphasized that only in one or two instances was water forced. A twenty-four-hour specimen of urine was collected, the dog being catheterized at the beginning and end of this period. When the phenolsulphonephthalein or other tests were performed, a portion of the urine collected by catheter was added to the total collection. It was observed in the first experiment that one of the most striking features was the accumulation of incoagulable nitrogen in the blood. Consequently, a nitrogen partition of the twenty-four-hour specimen of the urine was determined daily in conjunction with the frequent estimation of the incoagulable nitrogen in the blood. The total nitrogen in the urine was determined by the usual Kjeldahl-Gunning method, the urea by the method described by Marshall[17] and the ammonia nitrogen by Folin's aeration method. The urea and ammonia determinations were sometimes omitted because of putrefactive changes occurring in the urine in spite of the constant use of toluene. The urine was tested periodically for reducing substances with Fehling's solution and for albumin with the heat and acetic acid, and Heller's test. The urinary sediment was also examined at the same time for casts, cells, etc.

The phenolsulphonephthalein test of Rowntree and Geraghty was employed according to their original technic.[18] The urine was collected at the end of one or two hours, by catheter, and the percentage of the dye excreted determined colorimetrically. It is recognized that the residual urine lying behind the obstruction should have a tendency to decrease the absolute amounts of phenolsulphonephthalein recovered within a definite time after injection. To eliminate this factor as much as possible, water was forced as a routine, insuring free diuresis and rapid passage of urine into the bladder. This does not entirely correct the error, but it remains a constant one, and changes in the amounts of phenolsulphonephthalein and lactose recovered from the bladder indicate corresponding changes in the amounts excreted by the kidney.

The lactose test was carried out according to the method described by Schlayer,[19] 2 gm. being injected intravenously.

The phloridzin test, advocated of late years by Roth,[20] was used in the course of the experiments, 5 mg. being injected intramuscularly according to his technic.

The incoagulable nitrogen and urea content of the blood was determined at frequent intervals. The blood was taken according to the method used by Folin and Denis,[21] specimens being drawn into 5 c.c. pipets. One specimen of 5 c.c. for the estimation of incoagulable nitrogen was placed in a 50 c.c. measuring flask and 95 per cent. alcohol added up to the mark. The second specimen of 5 c.c. was run into a test-tube containing 1 c.c. of a 1 per cent. sodium oxalate solution; the urea content of this specimen was determined at

17. Marshall, E. K.: A Rapid Clinical Method for the Estimation of Urea in the Urine, Jour. Biol. Chem., 1913, xiv, 283.

18. Rowntree, L. G., and Geraghty, J. T.: The Phthalein Test, THE ARCHIVES INT. MED., March, 1912, p. 284.

19. Schlayer and Takayasu: Untersuchungen über die Function kranker Nieren, Deutsch. Arch. f. klin. Med., 1910, xcviii, 17.

20. Roth, Max: Welchen Wert hat die Phloridzinmethode für die Funtionelle Nierendiagnostic? Verhandl. d. deutsch. Gesellsch. f. Urol., Third Kongress, 1911, p. 192.

21. Folin, Otto, and Denis, W.: New Methods for the Determination of Non-Protein Nitrogen, Urea and Ammonia in Blood, Jour. Biol. Chem., 1912, xi, 527.

once according to Marshall's method.[22] This procedure being carried out so soon after withdrawal, the ammonia content of the blood could be neglected. After leaving the first specimen in 95 per cent. alcohol for at least twenty-four hours, the nitrogen content of the filtrate was determined, using the micro-method of Folin and Denis.[23] Their method was slightly modified in that to recover the ammonia after digestion, combined distillation and aeration was used instead of an air current.[23]

The depression of the freezing point in the blood-serum was determined with the Beckmann apparatus.

The histological technic was as follows: The tissues recovered at necropsy were fixed in 4 per cent. solution of formaldehyd. Sections were cut from paraffin blocks and stained in hematoxylin and eosin.

The following condensed protocol is given as illustrative of the usual course that followed ureteral obstruction. For the daily routine examination of the blood and urine, see Table 8.

Dog 19.—Black and white female, fox terrier, weight 7.75 kg. May 22, 1914: Urine shows nothing abnormal on routine clinical examination. Phenolsulphonephthalein, 88 per cent. in two hours. Lactose normally excreted in four hours. Total nitrogen in urine for past three days averaged 6.88 gm.

May 25, 9 a. m.: Blood analysis: Total incoagulable nitrogen 27 mg. and urea nitrogen 13 mg. per hundred c.c. of blood. 3 p. m.: Under ether anesthesia, left nephrectomy with placing of elastic band about right ureter 3 cm. above the bladder. General condition following the operation excellent.

May 30: The dog has made an excellent and rapid recovery from the operation five days ago. The wound has healed by first intention. The full allowance of food and water has been taken daily, and objectively the dog is perfectly normal. The phenolsulphonephthalein excretion has steadily diminished until to-day it is 35 per cent. in two hours; the blood nitrogen likewise increased until it now stands at 102 mg. per hundred c.c.; the urea nitrogen is 69 mg. per hundred c.c., being a well-marked increase in its percentage of the total nitrogen. The average daily output of urine has about doubled that recorded before operation. The daily excretion of nitrogen in the urine has remained practically the same, averaging 6.27 gm. in twenty-four hours.

June 5: For the past four days the dog has not taken its allowance of meat, but has drunk the full 300 c.c. of water. This is the only symptom of any possible general disturbance, the animal being quite lively. Lactose delayed until eight hours. Phenolsulphonephthalein excretion shows little change (30 per cent. in two hours). The incoagulable nitrogen in the blood has dropped to 76 mg. per hundred c.c. The dog has lost 450 gm. in weight since May 30, 1914. For the past two days the polyuria has almost ceased. The daily output of nitrogen in the urine has dropped to 3.58 gm. This corresponds fairly accurately to the lessened intake of nitrogen.

June 8: Weight, 7.15 kg. Nitrogen in blood has increased to 96 mg. per hundred c.c. Phenolsulphonephthalein excretion 25 per cent. in two hours; urine 260 c.c. in twenty-four hours, trace of albumin, no casts. Total nitrogen in urine has remained low, averaging 3.3 gm. despite the fact that the food intake has been practically normal for several days.

June 9: During the past twenty-four hours the dog passed but 90 c.c. of urine and has eaten only 30 gm. of meat. Despite the small volume of urine the specific gravity and the concentration of nitrogen is lower than that of the day before.

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22. Marshall, E. K.: A New Method for the Determination of Urea in Blood, Jour. Biol. Chem., 1913, xv, 487. Van Slyke, D. D.: A Method for Quantitative Determination of Aliphatic Amino Groups, Jour. Biol. Chem., 1911, ix, 185.

23. This method was devised by B. B. Turner and has been used in this laboratory for several months, and has proved very satisfactory. It will be published later.

June 12: The dog jumps about and is lively, but examination reveals early signs of distemper. Temperature 38 C. (100.4 F.), pulse 140. Lactose delayed until ten hours. Phenolsulphonephthalein, 16 per cent. in two hours. Blood (60 c.c.) withdrawn for nitrogen partition. This shows: total incoagulable nitrogen, 92 mg.; urea nitrogen, 53 mg.; amino-acid nitrogen,[22] 4 mg. per hundred c.c. Freezing point of serum, 0.59. Total twenty-four-hour urine output, 260 c.c., nitrogen in urine, 2 gm.

June 13, 1914: Dog killed by chloroform. Necropsy: Thorax shows no abnormality. Lungs and heart clear. Abdomen: No signs of infection about scar, peritoneum everywhere clean and glistening. No free fluid; all abdominal viscera appear normal except the right kidney and ureter. No scar tissue or signs of infection at the site of left nephrectomy. At the site of the rubber band is a fair amount of rather dense scar tissue. Above this point the ureter is thin walled, and markedly dilated; below it is normal in size and appearance.

The relation between the increased incoagulable nitrogen in the blood and the phenolsulphonephthalein excretion during the first few days of the experiment is well seen in Figure 1.

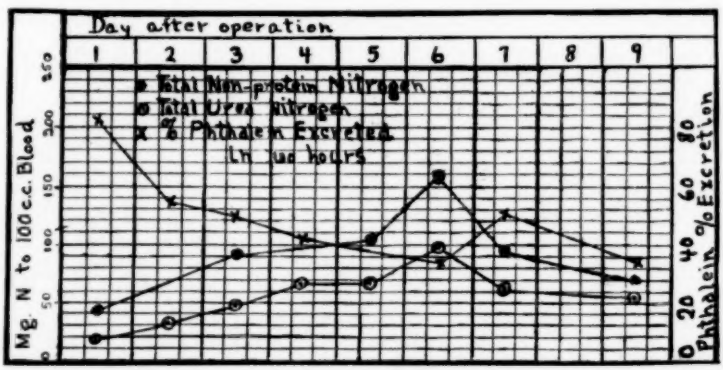

Fig. 1.—Relation between the increased incoagulable nitrogen in the blood and the phenolsulphonephthalein output during the first few days of the experiment with Dog 19.

COMMENT

The clinical course which followed the placing of a band about the ureter can be divided into two stages. During the first period the animals were objectively normal, the only evidences of derangement being a mild polyurea, a well-marked thirst, and the cumulative phenomena in the blood. The common symptoms of toxemia, such as loss of appetite, vomiting or diarrhea, appeared but rarely, the dogs being bright and lively. Indeed, two of them, Dogs 10 and 19, were almost abnormally so. The thirst was at all times present and was undoubtedly secondary to the polyuria, for the urinary output frequently exceeded the fluid intake over a period of several days at a time, as an examination of the tables will show. There was never any evidence of edema, but there was, in all cases, a steady, gradual loss

of weight. Determination of the number of red blood-cells and hemoglobin in Dogs 16 and 17 showed that there was no anemia. The second stage of the clinical course was the toxic period that preceded death, and it was of short duration, the longest being seven days. The characteristic features of the intoxication were loss of appetite, vomiting, progressive weakness, and the frequent passage of fluid stools containing mucus and traces of blood. There was definite slight trembling and muscular twitching. No convulsions were observed, but as most of the dogs died during the night, convulsions may have occasionally immediately preceded death. Drowsiness or

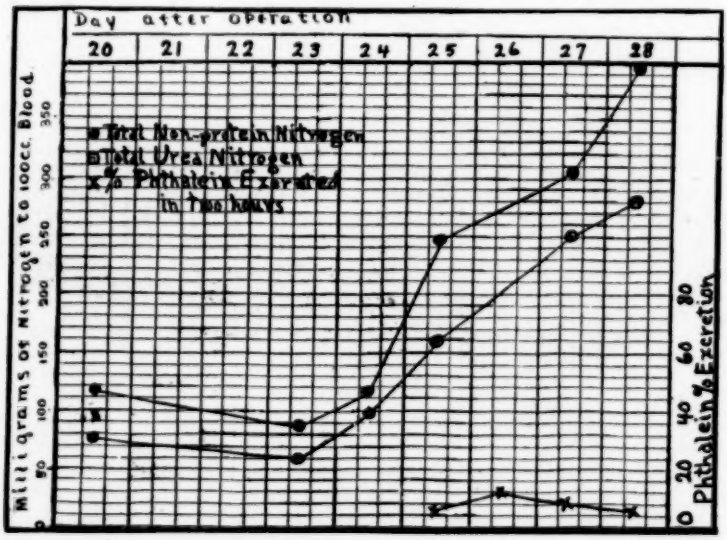

Fig. 2.—Relation between the increased incoagulable nitrogen in the blood and the phenolsulphonephthalein output a few days before death. Dog 10.

coma was certainly not present. Although very weak, the animals remained awake and seemed mentally alert. One animal was observed constantly for several hours before death, and utter weakness without dyspnea or irritative phenomena characterized the final picture. The respirations became gradually shallower and the pulse weaker until death occurred.

In brief, it seems that the establishment of a moderate back-pressure on the kidney had at first very little effect on the general condition of the dogs. There were, however, cumulative phenomena in the blood and changes demonstrable by functional tests, together with a mild polyurea. After a varying length of time there was a sudden

change, and a severe and rapidly fatal intoxication set in. During this period the functional tests indicated very marked renal insufficiency; examination of the urine together with the necropsy findings showed that pyelonephritis was present in every case.

The determination of the amounts of incoagulable nitrogen in the blood revealed striking changes. There was an immediate, sharp initial rise in the total incoagulable nitrogen, with a relatively greater increase in the urea nitrogen content. This urea nitrogen sometimes amounted to as much as 90 per cent. of the total. In general, following the first sharp rise, the nitrogen maintained a fairly constant level with but moderate fluctuations. This continued to within a few days of death, when, coincident with the development of the usual terminal symptoms, there was a great increase. The increase at this stage,

Fig. 3 (Dog 18).—The hydronephrotic kidney and the normal kidney (removed from opposite side) photographed on the same scale.

together with the low phenolsulphonephthalein output, are charted in Figure 2. There were, however, several important variations from this general type. Thus, Dog 17 showed a normal nitrogen content of the blood for sixteen days following the placing of the band about the ureter. In the suspicion that no obstruction had been created, an exploratory laparotomy was performed. It was found that at the site of the band a moderately thick ring of adhesions had formed. The ureter above this was definitely dilated and on palpation of the pelvis of the kidney, fluctuation was felt. The abdomen was at once closed and the observations continued as before. The determination of the incoagulable nitrogen in a sample of blood taken just before the operation showed 68 mg. per hundred c.c. Within seven days this had increased to 100 mg. per hundred c.c., and from then on there was a rapid rise until death. The question naturally arises as

to why, in this case, such an unusually long period elapsed before the cumulative phenomena appeared. Was it due to the fact that the hydronephrosis was mild and of slow development, or could it be that the obstruction was at first insufficient to produce any back-pressure, but later became so on account of contracting adhesions? Two facts indicate that the former was probably the case: First, there was a definite decrease in the phenolsulphonephthalein on the third and ninth days, showing that some change had taken place in the kidney; and second, at necropsy it was found that the pressure necessary to force fluid through the obstructed ureter amounted to 12 cm. of water —a very slight obstruction.

The most rapid rise occurred in Dog 16, in which the nitrogen content of the blood amounted to 168 mg. per hundred c.c. on the third

Fig. 4 (Dog 19).—The hydronephrotic kidney and the normal kidney (removed from opposite side) photographed on the same scale.

day after operation. At this time the animal was moderately toxic, vomiting several times. Venesection was performed on the fifth day, 225 c.c. of blood being removed. This was at once replaced by 150 c.c. of defibrinated blood, taken from a normal dog, and 100 c.c. of physiological saline solution. Within twenty-four hours there was a very sharp decrease in the incoagulable nitrogen, and from then until death, resulting from peritonitis, it was but slightly above normal. Associated with this rapid drop was a remarkable increase of the total nitrogen output in the urine.

The determination of the freezing point of the serum in a number of instances showed that there were but slight deviations from the normal when the nitrogen content was moderately increased; but with

the great accumulation of nitrogen preceding death the freezing point was considerably lowered.

The daily output of urine increased at once after the operation and continued so throughout the whole course. That this was a true polyuria is indicated by the fact that reducing the fluid intake did not immediately affect the total amount of urine. The specific gravity was correspondingly low. Faint traces of albumin appeared intermittently throughout. In the urine of but one dog (Dog 18) were casts found. The nitrogen output in the urine showed important variations. The average daily amount was approximately equal to the intake until the final stages, when a definite decrease is to be noted.

TABLE 1.—Intake and Output of Nitrogen During Non-Toxic Period

Dog	Time, days	Total Intake gm. N.	Average Daily Intake gm. N.	Total Urinary Output gm. N.	Average Daily Urinary Output gm. N.	Average Daily Loss of wt. gm.
10.....	16	80.9	5.05	85.17	5.32	37.5
17.....	21	99.1	4.58	82.3	3.92	76.2
18.....	25	101.3	4.05	98.1	3.92	44
19.....	19	62	3.26	68.1	3.58	71

TABLE 2.—Intake and Output of Nitrogen During Toxic Period

Dog	Time, days	Total Intake gm. N.	Average Daily Intake gm. N.	Total Urinary Output gm. N.	Average Daily Urinary Output gm. N.	Average Daily Loss of wt. gm.
10.....	4	0.6	0.15	11.19	2.79	387
17.....	6	6.47	1.08	15.8	2.63	250

In Table 1 is recorded the total amount of nitrogen excreted in the urine, as compared with that ingested, from the time of operation until the toxic symptoms developed; in the same manner the intake and output for the toxic period are shown in Table 2. In the case of Dogs 10 and 19 the output exceeded the intake, while with the other two the reverse took place. This bears no relation to the size of the animal or the loss of weight. The differences were slight, with one exception, Dog 17, in which the intake exceeded the output by 16.8 gm. This was not, however, accompanied by any marked increase in the non-protein nitrogen content of the blood.

During the terminal stages, although the nitrogen output greatly exceeded the intake, it did not equal the normal excretion during sim-

ple starvation.[24] This suggests that the great rise in the nitrogen content of the blood during this stage is due to a definite renal retention. A striking instance in which a low nitrogen excretion was accompanied by an accumulation of nitrogen in the blood is found in the case of

TABLE 3.—EXAMINATIONS—

Date	Day	Condition	Weight kg.	Intake		Blood			
				H_2O c.c.	N. gm.	Total Non-protein N. mg. per 100 c.c.	Urea N. mg. per 100 c.c.	Urea N. %	Δ
4/18	..	Normal	10.6	300	5.8	32	19	59	..
4/21	0	Operation	....	...	...	...	..	..	..
4/24	3	Good	....	300	5.8	122	86	70	..
4/25	4	Good	10.2	300	5.8	109	93	93	..
4/26	5	Refused food	....	600	1.8	116	103	88	..
4/27	6	Good	....	600	2.9	130	107	82	..
4/28	7	Good	....	600	5.8	126	..	..	..
4/29	8	Lively	....	800	5.8	99	56	56	..
4/30	9	Lively	9.7	800	5.8	110	64	58	..
5/ 1	10	Lively	9.5	400	5.8	132	92	70	..
5/ 2	11	Lively	9.5	400	5.8	104	69	66	..
5/ 3	12	Lively	9.5	300	5.8	...	..	..	..
5/ 4	13	Lively	9.4	300	5.8	100	87	87	..
5/ 5	14	Lively	9.3	300	5.8	...	..	..	..
5/ 6	15	Lively	....	450	5.8	116	78	68	.65
5/11	20	Lively	0.5	...	...	...	..	..	..
5/12	21	Lively	....	700	5.8	...	..	..	..
5/13	22	Lively	....	700	5.8	...	..	..	..
5/14	23	.....	9.6	700	5.8	86	59	69	..
5/15	24	Refused food	....	700	0.8	116	99	85	..
5/16	25	Vomiting	9.25	...	...	245	158	64	.75
5/17	26	Vomiting	8.45	...	...	...	...	..	..
5/18	27	Improved	....	300	0	306	250	82	.75
5/1[illegible]	28	Very sick	8.05	400	0.6	395	[illegible]80	71	.75
5/[illegible]	[illegible]	Died	....	...	..	...	...	..	..

Dog 16. On the third day after operation only 95 c.c. of urine were passed, despite the fact that water was forced. The nitrogen eliminated amounted to but 0.62 gm. Corresponding to this the incoagulable nitrogen in the blood rose from 66 to 178 mg. per hundred c.c.

24. Von Noorden, Carl: Metabolism and Practical Medicine, 1907, p. 292.

It was hoped that a careful study of the nitrogen intake and output might throw some light on the question as to whether the increase of incoagulable nitrogen in the blood is due to a (renal) retention or to metabolic disturbances characterized by an increased formation of

—OF DOG 10

Urine							Phthalein %		Lactose
Amt. c.c.	Sp. Gr.	Albumin	Sediment	N. gm.	Urea N. gm.	Urea N. %	1 hr.	2 hrs.	
240	1.030	0	Neg.	4.44	....	..	70	..	6 hours
...	.....	....	....	....	....	..	..	..	.....
...	.....	....	....	....	....	..	30	52	.....
350	1.020	0	Neg.	4.13	2.9	72	..	..	8 hours
550	1.020	....	....	6.41	4.65	73	..	..	.....
515	1.020	....	....	5.74	4.29	75	..	..	.....
600	1.018	Trace	W. B. C.	6.35	4.12	65	8	22	.....
580	1.012	....	....	6.00	3.81	62	..	..	8 hours
600	1.014	....	....	5.99	3.33	56	..	..	.....
515	1.010	....	....	5.08	....	..	..	..	.....
480	1.018	....	....	5.61	3.38	60	..	..	.....
425	1.020	....	....	4.64	....	..	..	..	.....
400	1.018	....	....	5.15	....	..	..	..	.....
405	1.022	Trace	Neg.	5.50	....	..	..	..	.....
405	1.023	....	....	5.39	....	..	21	38	.....
...	.....	....	....	....	....	..	..	37	.....
535	1.017	Trace	Neg.	5.24	....	..	..	..	.....
515	1.012	Trace	Neg.	4.39	....	..	..	..	.....
470	1.018	....	....	5.20	....	..	..	..	10 hours
395	1.018	Trace	Neg.	4.26	....	..	..	..	.....
630 (?)	1.010	Trace	Neg.	1.91	....	..	..	0	.....
430	1.018	Trace	Pus	3.90	2.63	68	..	12	.....
475	1.012	Trace	Pus	2.99	1.99	67	..	8	.....
700	1.020	Trace	Pus	2.39	98	39	..	.	.....
...	....	....	....	....	....	..	..	.	.....

nitrogenous bodies. Bradford,[25] studying the changes in the nitrogen of the blood and urine following the removal of from two-thirds to three-fourths of the total kidney substance, expresses the opinion that

25. Bradford, J. R.: The Results Following Partial Nephrectomy and the Influence of the Kidney on Metabolism, Jour. Physiol., 1898-9, xxiii, 415.

TABLE 4.—EXAMINATIONS—

Date	Day	Condition	Weight kg.	Intake		Blood			
				H_2O c.c.	N. gm.	Total Non-protein N. mg. per 100 c.c.	Urea N. mg. per 100 c.c.	Urea N. %	Δ
		Normal	4.8	...	...	...	26	..	..
4/ 2	..	Operation	....	...	...	...	..	..	..
4/ 4	2	Good	....	...	...	...	..	..	..
4/ 6	4	Vomited	....	...	...	...	..	..	..
4/ 7	5	No vomiting	....	500	...	...	90	..	..
4/ 8	6	Improved	....	300	5.8	112	77	69	..
4/ 9	7	Good	....	550	5.8	...	88	..	..
4/15	13	Good	....	400	5.8	70	35	50	..
4/16	14	Good	4.4	300	5.8	...	..	..	..
4/17	15	Good	....	300	5.8	...	..	..	..
4/18	16	Good	....	...	...	...	35	..	..
4/19	17	Good	....	165	5.8	...	..	..	..
4/20	18	.....	....	250	5.8	67	39	58	..
4/21	19	Exploratory	....	...	...	...	..	..	..
4/23	21	Good	4.6	500	5.8	...	..	..	..
5/ 1	29	Good	4.5	400	5.8	68	40	59	..
5/ 6	34	Sick	4.2	300	0	...	117	..	..
5/ 7	35	Sick	....	300	...	278	..	..	0.74
5/ 8	36	Died	....	...	...	...	..	..	..

TABLE 5.—EXAMINATIONS—

Date	Day	Condition	Weight kg.	Intake		Blood			
				H_2O c.c.	N. gm.	Total Non-protein N. mg. per 100 c.c.	Urea N. mg. per 100 c.c.	Urea N. %	Δ
5/ 3	..	Normal	10.7	300	5.8	30	9	30	.58
5/ 4	..	Operation	....	300	5.8	29	13	46	..
5/ 5	1	Good	....	235	0	46	31	68	..
5/ 6	2	Good	10.5	450	5.8	66	43	65	..
5/ 7	3	Vomited	....	300	5.8	178	124	70	..
5/ 8	4	Improved*	....	1,000	1.0	188	122	65	..
5/ 9	5	Phlebotomy transfusion	....	600	0	...	84	..	..
5/ 9	..	Three hours after.....	....	...	...	...	61	..	..
5/10	6	Improved	....	1,050	6.4	...	25	..	..
5/11	7	Onset of peritonitis.....	9.	400	0	84	24	28	..
5/12	8	Peritonitis	....	650	5.8	...	27	..	..
5/13	9	Peritonitis	8.9	600	5.8	41	25	62	..
5/14	10	.....	8.95	...	...	...	..	..	..
5/15	..	Died	....	...	...	...	..	..	..

* R. B. C., 6,200,000; Hb. 120 per cent.

—OF DOG 14

Urine							Phthalein %		Lactose
Amt. c.c.	Sp. Gr.	Albumin	Sediment	N. gm.	Urea N. gm.	Urea N. %	1 hr.	2 hrs.	
...	.....	0	Neg.	....	....	..	75	..	6 hours
...	.....	....	....	....	....	..	..	..	.....
...	1.025	Trace	Neg.	....	....	..	..	..	.....
275	1.030	0	Neg.	....	....	..	..	40	.....
...	.....	....	....	....	....	..	..	48	9.5 hrs.
400	1.012	Trace	W. B. C.	....	....	..	26	..	.....
475	1.020	Trace	Few W. B. C.	6.65	5.27	79	..	..	.....
...	.....	....	....	....	....	..	80	42	.....
...	.....	....	....	....	....	..	..	..	.....
190	1.025	Trace	Neg.	....	....	..	..	..	8 hours
...	.....	....	....	....	....	..	..	..	.....
335	1.018	Trace	Neg.	5.15	....	..	..	..	.....
325	1.022	Trace	Neg.	4.04	....	..	..	..	.....
...	.....	....	....	....	....	..	..	..	.....
450	1.020	Trace	Neg.	....	....	..	..	..	.....
...	.....	....	....	....	....	..	15	41	.....
310	1.013	Trace	Neg.	....	....	..	..	..	.....
185	.....	....	....	0.02	....	..	..	0	.....
...	.....	....	....	....	....	..	..	..	.....

—OF DOG 16

Urine							Phthalein %		Lactose
Amt. c.c.	Sp. Gr.	Albumin	Sediment	N. gm.	Urea N. gm.	Urea N. %	1 hr.	2 hrs.	
140	1.038	0	Neg.	5.90	....	..	65	..	6 hours
156	1.043	0	Neg.	6.68	....	..	..	..	.....
130	1.030	....	....	2.93	2.10	71	..	70	.....
420	1.023	Trace	Neg.	8.15	6.40	78	..	50	.....
95	1.010	0	Neg.	0.62	0.55	88	..	8	.....
780	1.010	Trace	Neg.	4.88	3.57	73	..	42	.....
565	1.010	Trace	Neg.	3.37	2.55	76	..	..	.....
...	.....	....	....	....	....	..	..	..	.....
1,060	1.018	0	Neg.	9.34	8.80	95	..	45	.....
375	1.021	0	Neg.	7.93	....	..	..	..	.....
345	1.032	0	Neg.	9.8	....	..	..	..	.....
395	1.036	0	Neg.	9.84	....	..	..	..	.....
...	.....	....	....	....	....	..	..	..	8 hours
...	.....	....	....	....	....	..	..	..	.....

TABLE 6.—Examinations—

Date	Day	Condition	Weight kg.	Intake		Blood			
				H_2O c.c.	N. gm.	Total Non-protein N. mg. per 100 c.c.	Urea N. mg. per 100 c.c.	Urea N. %	Δ
4/27	..	Normal	10.2	130	5.8	27	11	41	..
4/28	..	Normal	....	210	5.8	...	..	..	..
4/29	1	Operation	....	...	...	...	..	..	..
4/30	2	Good	....	300	0	38	17	47	..
5/ 1	3	Good	....	300	5.8	...	14	..	..
5/ 2	4		....	225	0	...	..	..	..
5/ 3	5		....	200	5.8	...	..	..	..
5/ 4	6		....	200	5.8	...	..	..	..
5/ 5	7		....	225	5.8	...	..	..	..
5/ 6	8		....	100	5.8	...	..	..	..
5/ 7	9		....	125	0	...	..	..	..
5/ 8	10	R. B. C. 7,200,000, Hb. 115 per cent.	....	220	5.8	...	..	..	..
5/ 9	11	Transfusion	....	300	5.8	...	12	..	0.62
5/10	12	Moderately sick	....	300	6.3	...	21	..	..
5/11	13	Improved	....	320	0	...	9	..	..
5/12	14	Good	9.35	220	5.8	...	..	..	..
5/13	15	Good	....	200	5.8	...	..	..	..
5/14	16	Exploratory	....	200	5.8	68	38	56	..
5/15	17	Good	....	300	0	...	27	..	..
5/16	18	Pulse 140, Temp. 39 C.	....	300	5.8	44	17	40	..
5/17	19	Good	....	400	5.8	...	..	..	..
5/18	20	Good	....	275	5.8	...	..	..	..
5/19	21	Pulse 122	9.2	450	5.8	...	..	..	..
5/20	22	Pulse 140, Temp. 41 C.	....	300 (?)	5.8	...	..	..	..
5/21	23	Refused to eat	....	500	5.8	100	62	63	..
5/22	24	Improved	8.6	400	1.7	110	74	67	..
5/23	25	Improved	....	500	2.9	98	71	73	..
5/24	26	Good	8.85	400	0.87	...	..	..	..
5/25	27	Good	....	200	1.0	136	86	64	..
5/26	28	Vomited	....	330	...	...	..	..	..
5/27	29	Vomiting	....	300	...	185	131	71	..
5/28	30	Sick	....	300	...	220	141	64	..
5/29	31	Very sick	7.1	...	...	...	..	..	..
5/30	32		....	500	...	...	..	..	..
5/31	33		....	300	0	...	..	..	..
6/ 1	34	Died	....	...	...	...	..	..	..

—OF DOG 17

Urine							Phthalein %		Lactose
Amt. c.c.	Sp. Gr.	Albumin	Sediment	N. gm.	Urea N. gm.	Urea N. %	1 hr.	2 hrs.	
115	1.050	0	Neg.	5.72	4.49	78	63	..	6 hours
135	1.043	0	Neg.	5.59	....	..	..	..	.....
...	.....	....	....	....	....	..	..	..	.....
?	1.060	0	Neg.	....	....	..	..	..	.....
245	1.025	Trace	Neg.	5.69	4.56	79	27	68	.....
150	1.022	....	....	3.05	2.24	73	..	..	.....
225	1.028	....	....	4.04	....	..	..	..	.....
230	1.030	....	....	2.74	....	..	..	..	.....
195	1.030	0	Neg.	6.42	....	..	..	..	.....
170	1.034	....	....	5.64	....	..	..	..	.....
110	1.035	....	....	3.83	....	..	41	..	.....
125	1.040	....	....	4.19	....	..	..	..	.....
150	1.030	....	....	4.18	....	..	..	..	.....
130	1.026	....	....	2.55	1.82	71	..	..	.....
335	1.015	....	....	3.72	2.68	72	..	..	.....
105	1.032	....	....	3.10	....	..	..	..	.....
235	1.020	0	Neg.	3.40	....	..	..	..	.....
235	1.020	Trace	Neg.	3.72	....	..	..	..	.....
130	1.032	....	....	2.46	....	..	..	34	.....
215	1.015	....	....	4.40	....	..	..	37	.....
250	1.020	....	....	4.34	....	..	..	..	.....
205	1.024	....	....	3.96	....	..	..	..	.....
280	1.020	....	....	5.94	....	..	..	35	8 hours
385	1.010	....	....	2.40	....	..	..	..	.....
265	1.018	Trace	Pus cells	2.55	1.15	51	..	..	.....
440	1.017	....	....	3.72	2.15	58	..	20	.....
385	1.016	....	....	3.39	1.46	43	..	..	.....
295	1.017	....	....	2.35	....	..	..	..	.....
190	1.014	....	....	1.52	.59	38.8	..	..	.....
265	1.018	+	W. B. C.	1.82	1.05	58	..	..	.....
315	1.018	....	....	3.00	....	..	..	..	.....
?	.....	....	....	....	....	..	..	5	.....
?	.....	....	....	....	....	..	..	..	.....
280	1.020	....	....	2.87	....	..	..	..	.....
300	1.010	+	Pus	0.97	....	..	..	..	.....
...	.....	....	....	....	....	..	..	..	.....

TABLE 7.—EXAMINATIONS—

Date	Day	Condition	Weight kg.	Intake		Blood			
				H_2O c.c.	N. gm.	Total Non-protein N. mg. per 100 c.c.	Urea N. mg. per 100 c.c.	Urea N. %	Δ
5/22	..	Normal	5.15	300	5.8	...	..	..	..
5/23	..	Normal	....	300	5.8	34	14	41	..
5/24	..	Normal	....	300	5.8	...	..	..	..
5/25	..	Operation	....	...	...	...	...	..	..
5/26	..	Before operation	....	0	0	...	..	..	..
5/26	1	After operation	....	200	0	39	20	52	..
5/27	2	Good	....	300	3.2	55	27	50	..
5/28	3	Good	....	400	5.8	56	30	54	..
5/29	4	Good	....	300	5.8	74	43	58	
5/30	5	Good	5.15	300	5.8	72	44	61	..
5/31	6	Good	....	250	3.8	...	..	..	..
6/ 1	7	Good	....	300	5.8	86	33	38	..
6/ 2	8	Good	....	300	4.6	...	..	..	..
6/ 3	9	Good	....	300	4.2	95	40	42	..
6/ 4	10	Good	....	300	4.2	...	..	..	..
6/ 5	11	Good	4.7	300	5.8	108	68	63	..
6/ 6	12	Good	....	300	3.8	...	..	..	..
6/ 7	13	.....	....	300	3.8	...	..	..	..
6/ 8	14	.....	4.65	300	4.6	90	49	54	..
6/ 9	15	.....	....	300	1.5	...	..	..	..
6/10	16	.....	4.75	300	4.9	...	43	..	..
6/11	17	.....	4.55	300	3.3	...	..	..	..
6/12	18	Distemper	4.45	300	1.6	84	42	50	..
6/13	19	Distemper	4.40	300	3.8	...	..	..	..
6/14	20	Distemper	4.25	150	1.0	...	..	..	..
6/15	21	Distemper	4.15	300	0.9	68	28	41	..
6/16	22	Distemper	4.05	300	5.8	...	..	..	..
6/17	23	Distemper	4.05	300	5.8	...	..	..	..
6/18	24	Distemper	4.05	300	5.8	92	48	52	.56
6/19	25	.....	....	200	5.8	114	60	53	.60
6/20	1	Sacrificed	....	...	...	...	..	..	..

* Probable decomposition of urea after voiding.

—OF DOG 18

Urine									Phthalein 2 hrs. %	Lactose
Amt. c.c.	Sp. Gr.	Albumin	Sediment	N. gm.	Urea N. gm.	Urea N. %	NH_3-N. gm.	NH_3-N. %		
215	1.025	0	Neg.	4.82	3.78	78	...	....	95	6 hrs.
235	1.020	0	Neg.	4.51	3.22	71	.21	4.6	..	.....
215	1.023	0	Neg.	4.65	3.66	79	.26	5.5	..	.....
...	.....	....	....	....	....	..	...	....	..	.....
21	.....	....	....	0.52	0.37	71	...	....	..	.....
80	1.020	0	Neg.	0.86	0.49	58	...	....	85	.....
85	1.040	0	Few casts	2.88	....	..	...	....	40	.....
175	1.030	Trace	Neg.	5.41	3.66	68	.5	9.3	62	.....
320	1.027	0	Neg.	7.48	5.58	75	.78	10	55	.....
255	1.025	0	Neg.	5.52	3.94	77	...	....	58	.....
180	1.025	Trace	Neg.	3.85	3.30	86	.39	10	..	.....
300	1.020	0	Neg.	4.91	3.82	80	.19	4	52	.....
295	1.020	0	Neg.	4.23	3.47	82	.23	5.5	..	.....
500	1.028	0	Neg.	7.96	5.16	65	.57	12	75	.....
350	1.020	Trace	Neg.	4.73	4.13	87	...	....	..	8 hrs.
560	1.018	Trace	Neg.	6.74	4.67	69	.87	13	45	.....
410	1.015	Trace	Neg.	5.05	3.73	73	.51	6.2	..	.....
230	1.020	Trace	Neg.	0.03	2.00	67	.94	31*	..	.....
290	1.018	Trace	Neg.	3.41	1.93	57	...	....	35	.....
255	1.012	Trace	Neg.	2.32	1.07	42	.53	23*	..	.....
400	1.018	0	Neg.	3.54	2.75	72	.48	12	35	.....
325	1.012	Trace	Neg.	3.18	2.05	64	.43	13	..	.....
155	1.015	Trace	Neg.	1.67	1.08	65	.19	11	15	8 hrs.
245	1.015	Trace	Neg.	2.75	1.59	58	...	....	20	.....
255	1.015	Mod.	Neg.	2.37	1.95	82	...	....	..	.....
285	1.014	+	Pus	1.96	1.52	77	.14	7	..	.....
380	1.020	+	Pus	4.92	3.66	74	.30	6	..	.....
300	1.022	+	Pus	4.62	3.43	74	.43	9	43	.....
295	1.025	+	Pus	4.61	3.71	80	...	....	38	.....
280	1.024	+	Pus	....	....	..	...	....	50	.....
...	.....	....	....	....	....	..	...	....	..	.....

the increased content in the blood is due to an excessive breaking down of tissue. Pearce,[26] studying the nitrogen excretion following the removal of three-fourths of the total kidney substance, states that no change takes place in the nitrogen metabolism other than that due to an inanition which results from the gastro-intestinal irritation constantly associated with extensive kidney reduction. We do not feel

TABLE 8.—EXAMINATIONS—

Date	Day	Condition	Weight kg.	Intake		Blood			
				H_2O c.c.	N. gm.	Total Non-protein N. mg. per 100 c.c.	Urea N. mg. per 100 c.c.	Urea N. %	Δ
5/22	..	Normal	7.75	250	5.8	...	..	..	..
5/23	..	Normal	....	150	5.8	...	..	..	..
5/24	..	Normal	....	75	5.8	27	13	49	..
5/25	..	Operation	....	...	...	...	..	..	..
5/26	..	Before operation	....	200	0	...	..	..	..
	1	After operation	....	0	0	41	19	46	..
5/27	2	Good	....	300	5.8	...	29	..	..
5/28	3	Very lively*	....	400	5.3	90	46	51	..
5/29	4	Very lively	....	300	5.8	...	69	..	..
5/30	5	Very lively	....	300	5.8	102	69	68	..
5/31	6	Very lively	....	250	4.2	160	96	60	..
6/ 1	7	Very lively	7.20	300	1.3	96	63	66	..
6/ 2	8	Very lively	....	300	1.9	...	..	..	..
6/ 3	9	Very lively	....	300	3.9	68	53	78	..
6/ 4	10	Very lively	....	300	0.4	...	..	..	..
6/ 5	11	Very lively	7.20	300	5.8	76	43	57	..
6/ 6	12	Very lively	7.20	300	4.2	...	..	..	..
6/ 7	13	Very lively	7.20	300	5.8	...	..	..	..
6/ 8	14	Very lively	7.15	300	3.3	96	48	50	..
6/ 9	15	Very lively	7.00	300	0.9	94	41	44	..
6/10	16	Very lively	6.90	280	3.7	...	66	..	..
6/11	17	Very lively	6.80	315	1.0	...	..	..	..
6/12	18	Distemper	6.55	225	0.6	92	53	58	.59
6/13	19	Distemper	6.40	300	2.9	108	57	53	.66

* See protocol.

that in our own experiments the nitrogen determinations during the non-toxic period offered conclusive evidence on this point,[27] although

26. Pearce, R. M.: Influence of a Reduction of Kidney Substance on Nitrogenous Metabolism, Jour. Exper. Med., 1908, x, 632.

27. Further work is planned for the study of this important point.

in several instances the tables show (particularly 7 and 8) nitrogenous equilibrium or even nitrogenous loss associated with a rise in the non-protein nitrogen of the blood. This would indicate an increased protein catabolism. During the terminal stages, however, there was a definite reduction in the nitrogen eliminated, indicating that the cumulative phenomena are due, in part at least, to retention.

—OF DOG 19

Urine									Phthalein 2 hrs. %	Lactose
Amt. c.c.	Sp. Gr.	Albumin	Sediment	N. gm.	Urea N. gm.	Urea N. %	NH_3-N. gm.	NH_3-N. %		
125	1.050	0	Neg.	6.09	4.90	80	...	....	..	.....
155	1.050	0	Neg.	8.81	6.09	69	...	....	88	4 hrs.
135	1.045	0	Neg.	5.74	5.30	92	.25	4.3	..	.....
?	.....	....	....	....	....	..	...	....	..	.....
23	.....	....	....	0.66	0.48	70	...	....	..	.....
65	1.055	0	Neg.	2.42	1.69	70	...	....	82	.....
230	1.030	0	Neg.	7.57	6.12	81	...	....	54	.....
240	1.025	0	Neg.	5.34	4.12	77	.38	7	50	.....
340	1.025	Trace	Neg.	5.35	4.71	88	.64	12	42	.....
380	1.020	0	Neg.	6.81	5.14	75	.57	8.4	..	.....
230	1.017	Trace	Neg.	2.51	1.94	77	.17	6.8	33	.....
395	1.018	0	Neg.	5.25	4.40	84	.44	8.2	50	.....
255	1.018	Trace	Neg.	3.62	2.73	75	.37	9	..	.....
235	1.022	Trace	Neg.	3.98	3.02	76	.35	9	35	.....
160	1.020	Trace	Neg.	2.57	2.06	80	.23	9	..	8 hrs.
265	1.023	Trace	Neg.	4.08	2.61	64	.41	10	30	.....
225	1.021	Trace	Neg.	3.22	2.81	87	.37	11	..	.....
260	1.020	Trace	Neg.	2.80	2.45	87	...	....	..	.....
260	1.018	Trace	Neg.	3.13	2.26	72	.34	11	15	.....
90	1.013	Trace	Neg.	0.87	0.64	73	.13	15	..	.....
215	1.016	Trace	Neg.	2.12	1.48	69	.23	11	26	.....
200	1.012	Trace	Neg.	2.00	1.24	62	.11	6	..	.....
200	1.016	Trace	Neg.	1.83	1.60	87	...	....	16	10 hrs.
227	1.018	Trace	Neg.	2.19	1.51	69	.26	16	14	.....

The phenolsulphonephthalein test has proved to be very sensitive in these cases, since in the earliest stages there is a slowing of the excretion and in the later stages a progressive reduction in the total. Normally in dogs there is excreted during the first hour from 60 to 70 per cent. of the amount injected, while during the second hour

an additional 15 to 20 per cent. is recovered. The first change noted in these cases was a reduction of the amount excreted in the first hour with a corresponding increase during the second hour, the total for two hours thus approaching normal. In the case of four of the dogs the phenolsulphonephthalein test was made daily following operation, and it is seen that within forty-eight hours there was a moderate reduction, the average total being 53 per cent. This corresponds to the increased nitrogen content of the blood. Coincident with the development of toxic symptoms, or with a marked diminution of urinary nitrogen, there was a low total excretion without exception. This is very striking. Attention is called to the suddenness with which marked functional changes took place in several instances. Thus, in Dog 16, within twenty-four hours the total phenolsulphonephthalein excretion dropped from 50 per cent. to 3 per cent., and during this time toxic symptoms appeared. At the end of the next twenty-four hours the general condition was improved and the phenolsulphonephthalein excretion was 42 per cent.

The only deviation from normal in the excretion of lactose was a moderate delay, the longest being ten hours.

The phloridzin test was performed as follows: Dog 14, on the second, fourteenth and twenty-fourth days after the operation; Dog 10, on the seventh and twentieth days, and Dog 18, on the twenty-fourth day. Without exception reducing bodies were present in the urine in large amounts before the expiration of half an hour from the time of injection. This corresponds with the normal as determined before the operation in each case.

PATHOLOGICAL CONSIDERATION

In each of the eight experiments a hydronephrosis developed as a result of the ureteral obstruction. The pressure necessary to overcome this resistance varied from 12 to 70 cm. of water. In every case, grossly, the ureter was tortuous and markedly dilated from the kidney to the point of obstruction, and the kidney was larger than the one previously removed from the opposite side, with dilatation of the pelvis and flattening of the calices. The distention of the capsular veins was always prominent, but varied considerably in degree. Thus, in Dog 18, the capsule was smooth and normal in color, only a vein here and there being noticeably engorged; while, on the other hand, the kidney of Dog 19 was covered with a network of large and tortuous vessels. In one instance, Dog 16, the kidney showed, microscopically, a beginning atrophy of the parenchyma, with only a slight dilatation of the collecting tubules, although, in the gross, the pelvis was distended and the calices flattened.

Infection of the pelvis of the kidney occurred in five of the eight dogs studied. It is significant that those which did not develop an infection had the shortest duration of life, after operation. Four cases, 10, 14, 17 and 18, showed pus in the urine for several days before death, and in these the pyelonephritis was very marked. In the remaining animal, Dog 19, the infection was slight, and the urine showed no pus. In Dogs 14, 18 and 19, there were no signs of cystitis. Thus it will be seen that in those cases in which sufficient time elapsed a pyelonephritis developed, and that three were unaccompanied by cystitis.

CONCLUSIONS

1. Incomplete ureteral obstruction in dogs, causing a back pressure of from 12 to 30 cm. of water, results in the development of a hydronephrosis.

2. This hydronephrosis causes a definite disturbance of renal function, characterized by polyuria, traces of albumin, diminished output of phenolsulphonephthalein and delayed excretion of lactose. There is no delay in the appearance of a glycosuria after the injection of phloridzin.

3. When one kidney is removed from an animal and the foregoing functional changes are brought about in the remaining organ, by the production of a hydronephrosis, the non-protein nitrogen content of the blood rises, and remains at this increased level (with slight variations) for a considerable period of time, unassociated with toxic symptoms.

4. This gives place to a sudden, severe, renal insufficiency, rapidly fatal, and characterized by marked toxemia, great increase in nitrogen content of the blood and very low phenolsulphonephthalein output.

5. During this final stage of renal insufficiency, caused by back-pressure alone, or by back-pressure with superimposed infection, there is a true nitrogen retention.

6. Under the conditions established in these experiments the occurrence of pyelonephritis is only a question of time; the animals which came to necropsy within ten days of the operation showed no signs of infection.

We wish to express our gratitude to Dr. L. G. Rowntree for his interest and helpful suggestions, and to Dr. M. C. Winternitz for his kindness in examining the pathological specimens and dictating the histological notes.

APPENDIX: HISTOLOGICAL NOTES ON THE AFFECTED KIDNEYS

Dog 10.—Marked, general, polymorphonuclear infiltration, the infection ascending from the pelvis and invading the cortex, overshadowing other changes that may be present. Definite dilatation of the glomeruli, with retraction of the tufts, and apparently some dilatation of the tubules.

Dog 14.—Infection in the pelvis, ascending into the pyramids, where there is a deposition of calcium salts. The pyramids are moderately flattened and the tubules dilated. In the cortex there are a few areas in which the tubules are dilated and filled with material suggesting forming casts. For the most part, in the cortex, the tubules are not widened, the lumina being small, and the epithelium somewhat swollen. One small but typical arteriosclerotic scar is seen.

Dog 16.—There is a striking beginning atrophy of the cortex, with a uniform decrease in size of the tubules. The glomeruli remain unchanged. Slight dilatation of the pyramid tubules. No signs of infection in the pelvis.

Dog 17.—Severe infection of the pelvis, ascending into the cortex, and obscuring other changes. There is seen, however, to be definite dilatation of the glomeruli with shrinking of the tuft.

Dog 18.—There is marked infiltration with polymorphonuclear leukocytes, running in streaks from the cortex to the pelvis. The glomeruli are moderately dilated, the capsular space being more conspicuous than usual. The tubules are everywhere dilated, without any flattening of the epithelium, the latter being swollen and coarsely granular, with irregular and serrated edges. In the lumen is a small amount of serum.

Dog 19.—There is a very slight infection in the pelvis and pyramids. The pyramidal tubules are less dilated than are the cortical ones. Just beneath the capsule there is a definite fibrosis of the cortex, and in this zone most of the glomeruli and tubules are atrophied, although there remain a few dilated canals. In the rest of the cortex the tubules are considerably dilated, the epithelium flattened and the lumina contain granular material. The glomeruli are widely distended and the tufts retracted. There are seen a few fibrous scars along the course of the interlobular vessels, but there is no arterial thickening.

FURTHER OBSERVATIONS ON THE EMPLOYMENT OF SPECIFIC AND NON-SPECIFIC ANTIGENS IN THE PERFORMANCE OF THE GONOCOCCIC COMPLEMENT-FIXATION TEST *

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In a former paper[1] read before the Philadelphia County Medical Society May 28, 1913, it was conclusively shown by Thomas and Ivy in an analysis of over 200 cases in which monavalent, trivalent, hexavalent and a commercial antigen of twelve strains of gonococci were employed, that the gonococcus complement-fixation test possesses great specificity so far as positive results are concerned. The results have proved that "the different strains of the gonococcus differ markedly one from another — so much so that the antibodies produced in the body by the toxin of one strain will in many instances not bind the complement in the presence of an antigen prepared from another strain. Therefore, if only one strain is used in the preparation of the antigen, a great many negative results would be obtained in positive cases; an antigen prepared from many strains fixes the complement whenever one of its component strains does so, and consequently the necessity of testing a serum against a number of antigens separately is avoided. It is not to be denied that there probably are other strains of gonococci differing widely from any present in the polyvalent antigen, so that at times a negative result will be obtained in a positive case."

Convinced from our previous study of the specificity of the gonococcus complement-fixation test in gonorrheal infections, namely, that although a negative reaction may be obtained in gonorrheal subjects and consequently is devoid of reliance, a positive reaction is most dependable and was not obtained in a large series of infectious and other diseases.

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* Read before the Philadelphia Pathological Society, May 28, 1914.

* From the Department of Genito-Urinary Surgery and Laboratories, Polyclinic Hospital, and the William Pepper Laboratory of Clinical Medicine.

1. Thomas, B. A., and Ivy, Robert H.: The Gonococcus Complement-Fixation Test and Analysis of Results from its Use, THE ARCHIVES INT. MED., 1914, xiii, 143.

In this article, in view of the finding of many Gram-positive and Gram-negative bacteria in the urine after massage of the prostate gland and seminal vesicles in the involvement of these organs in neisserian infection, a study has been made with respect to determining the specificity of the gonococcus antigen in the complement-fixation test by employing non-specific antigens made up from the various bacteria isolated from time to time.

Antigens were prepared from the following micro-organisms and utilized routinely in a series of serums from gonorrheal subjects:

Nine strains of gonococci.[2]
Fifteen strains of meningococci.[2]
Six strains of streptococci.
Six strains of the *Micrococcus albus*.
Six strains of the pneumococcus.
Six strains of *Micrococcus aureus*.
Three strains of the *Micrococcus catarrhalis*.[2]
Six strains of *Corynebacterium pseudodiphtheriticum*.
Six strains of *Bacillus coli*.

TECHNIC OF THE PREPARATION OF THE ANTIGENS

As in the former work the best results were obtained with antigens prepared in the following manner:

Forty-eight-hour old cultures were washed off in sterile distilled water, shaken for one hour, and autolyzed for twenty-four hours in a thermostat at the temperature of 37 C. and heated in a water-bath at 60 C. for one-half hour. Before use this antigen is diluted 1:10 by the addition of 0.85 per cent. salt solution. The quantities of each antigen used is determined by preliminary standardization. The technic on which we have learned to place the greatest reliance is essentially the same as that employed by us in the performance of the Wassermann reaction — substituting the specific or non-specific antigen in each case for the syphilitic antigen, using always the carefully standardized single unit of complement and the routine standardization of antigen and amboceptor. This technic is fully described in the former paper on this subject.

Two hundred and sixteen serums in all were tested by the employment of various non-specific antigens. These added to the results of the previous work number 420 serums in which the complement-fixa-

2. We are indebted to Dr. Parks of the Research Laboratory, New York Department of Health, for the fifteen strains of meningococci and the three strains of *Micrococcus catarrhalis*, and to Dr. A. P. Hitchens of H. K. Mulford Company for the nine strains of gonococci employed in this work.

tion test has been employed, using specific gonococcus and non-specific antigens.[3]

Of the 216 cases in which both the specific and non-specific antigens were employed, we have grouped the cases according to their clinical diagnoses.

1. Patients clinically cured, 9 cases.
2. Acute anterior urethritis, 10 cases.
3. Acute and subacute anteroposterior urethritis, 40 cases.
4. Chronic posterior urethritis, 84 cases.
5. Stricture, 7 cases.
6. Epididymitis, 30 cases.
7. Arthritis, 30 cases.
8. Gynecological affections, 3 cases.
9. Vulvovaginitis, 1 case.
10. Sexual impotence, 2 cases.

RESULTS OF COMPLEMENT-FIXATION REACTIONS WITH SPECIFIC GONOCOCCIC AND NON-SPECIFIC ANTIGENS IN TWO HUNDRED AND SIXTEEN CASES

Antigens	No. Cases	Results	
		No Positive	No. Negative
Specific; Gonococcic:			
Nonovalent	216	67	149
Parke, Davis & Co.	216	67	149
Non-Specific:			
Micrococcus catarrhalis	180	5	175
Pneumococcus	216	4	212
Micrococcus aureus	216	3	213
Streptococcus	216	1	215
Corynebacterium pseudodiphtheriticum	160	1	159
Meningococcus	216	1	215
Micrococcus albus	216	....	216
Bacillus coli	160	....	160

Of this series of cases 135 serums gave negative results with the employment of specific and non-specific antigens.

Sixty-seven serums gave positive results with specific gonococcus antigens.

Fifteen serums gave positive results with non-specific antigens.

Of the complement-fixation tests, using non-specific antigens, the *Micrococcus catarrhalis* antigen gave positive results in 5 cases, the pneumococcus in 4, the *Micrococcus aureus* in 3, the streptococcus in 1, the *Corynebacterium pseudodiphtheriticum* in 1 and the meningococcus in 1 case.

3. Standardization of all the specific and non-specific antigens at the conclusion of this study as compared with their antigenic properties in the beginning demonstrated no deterioration.

Four of the foregoing non-specific antigens gave positive results when all other non-specific and specific antigens resulted negatively. They were:

1. Pneumococcus, 4 cases.
2. *M. aureus,* 3 cases.
3. *M. catarrhalis,* 1 case.
4. *Corynebacterium pseudodiphtheriticum,* 1 case.

Six of the foregoing fifteen non-specific fixation reactions occurred conjointly with the specific fixation reaction. They were:

The *Micrococcus catarrhalis,* 4 cases.

The streptococcus, 1 case.

The meningococcus, 1 case.

Our explanation for these occurrences in the complement-fixation reaction is that frequently a mixed infection complicates the gonorrheal urethritis, prostatitis, seminal vesiculitis, etc., also that not infrequently the gonococcus has ceased to be viable and that the active cause for the inflammation is a superimposed bacterium.

CONCLUSIONS

1. Although mixed infections are commonly found, antibodies of the non-specific organisms rarely bind complement in the presence of the non-specific antigens, and when such is the case, it can be attributed to the implantation of a superimposed mixed infection.

2. The specificity of the gonococcus complement-fixation test when positive in cases of neisserian infection seems to be clearly established; a negative reaction, on the contrary, means absolutely nothing from the clinical point of view.

3. Those organisms in cases of mixed infection capable of binding complement in our studies have been the *Micrococcus catarrhalis,* the pneumococcus, the *Micrococcus aureus,* the streptococcus, the *Corynebacterium pseudodiphtheriticum* and the meningococcus.

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HOW SHALL WE TELL WHETHER OR NOT THE MYOCARDIUM IS COMPETENT?*

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The determination of the functional capacity of the vital organs is a problem that is of the utmost interest in prognosis. If a man consults a physician for symptoms pointing to disturbance of the heart, the kidneys or the liver it would be of great advantage not only to the patient, but also to his advisor if some satisfactory means were known by which the power of the affected organ to do its work could be determined. So far as concerns the kidneys and the liver, fairly reliable functional tests are at our disposal. Are we able to say as much of the myocardium? For example, a man, aged 50 or more years, presents himself in the consulting room complaining of dyspnea, or perhaps of some symptom less definitely associated with myocardial insufficiency. He proves to be a modern business man with important obligations. He has lived the life of his class: He has been a large and irregular eater and his diet has contained an overproportion of protein or of carbohydrate food, depending on his individual preference; he has drunk little or no water, two or three or more cups of coffee or tea, or of coffee and tea; more or less alcohol; sometimes malt liquors, sometimes distilled liquors, sometimes wine, again a liberal amount of all. He has smoked from eight to ten cigars a day. He has always slept well; but perhaps now he is beginning to have trouble in getting to sleep, or, provided he goes to sleep promptly, he soon wakens and is restless. His bowels, which have always been regular, are beginning to require attention. He has to get up once or twice at night to urinate, and for thirty years he has not taken any more exercise than was absolutely necessary. In the course of the physical examination you find him to be overweight; you find that he is beginning to develop a definite pulmonary emphysema; that his heart is larger than it should be and that the rate is a little accelerated, but that it presents no endocardial murmurs; that his blood-pressure is a trifle higher than it should be, and that his urine is increased in quantity and is of low specific gravity, but shows neither albumin nor casts. Let us suppose that the cardiac hypertrophy in such a case seems to be the important

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pathologic finding; can we determine by any means the capacity of the myocardium of that individual?

The following tests have been advocated from time to time for this purpose:

1. The increase in the pulse-rate between the recumbent posture and the erect posture.

2. The increase in the pulse-rate after slowly flexing and extending the right forearm (*Selbsthemmungsprobe* of Herz).

3. The increase of the systolic blood-pressure on constricting the fermoral arteries, proposed by Katzenstein.

4. The increase of the systolic blood-pressure after certain exercises, proposed by Graupner.

The determination of the change in pulse-rate on assuming the erect from the recumbent posture and after flexing and extending the right forearm a definite number of times is clinically easy of execution and may be applied equally well to patients of both sexes. The determination of increase of the systolic blood-pressure after constriction of the femoral arteries is less readily performed and is impossible in the case of female patients who are being examined in the physician's office. The procedure of Graupner requires a piece of apparatus which is not well adapted to the ordinary consulting room.

With the introduction of the auscultatory method of blood-pressure determinations it has been possible clinically to determine the diastolic pressure, and consequently the pulse-pressure, with accuracy. Hence it has become possible to determine certain mathematical formulas which indicate the conditions under which the circulation is being carried on.

Tigerstedt[1] has suggested a formula for determining the efficiency of the heart as a pump. The pulse-pressure multiplied by the pulse-rate gives the velocity of the circulation. The systolic pressure multiplied by the pulse-rate gives the work of the heart. The velocity of the circulation divided by the work of the heart, according to Tigerstedt, gives the efficiency of the heart as a pump.

$$\frac{\text{Pulse-pressure} \times \text{pulse-rate} = \text{velocity}}{\text{Systolic pressure} \times \text{pulse-rate} = \text{work}} = \text{efficiency of the heart as a pump.}$$

In other words, the pulse-pressure, divided by the systolic pressure. In a normal person this coefficient is from 25 per cent. to 35 per cent. In a normal person in whom the systolic pressure was 126 mm. and the diastolic pressure was 81 mm. obtained by the auscultatory method, the pulse-pressure was 45 mm. and the cardiac efficiency was 35 per cent.

1. Tigerstedt: In Hirschfelder: Diseases of the Heart and Aorta, 1910, Ed. 1, p. 26.

Many authors have agreed that the second phase (the murmur phase) of the auscultatory blood-pressure observation indicates cardiac strength (Tornai,[2] Fischer,[3] Goodman and Howell[4]).

Goodman and Howell[4] have shown that the second and third phases of the auscultatory blood-pressure indicate cardiac strength, and that the first phase and the fourth phase indicate cardiac weakness. They have suggested that by determining the percentage of the pulse-pressure formed by the different phases and adding the second and third phases together and the first and fourth phases together, a proportion could be determined which would give an idea of the relative cardiac strength and cardiac weakness factors. They found that when the cardiac weakness factor was in excess of the cardiac strength factor there was evidence of inefficiency of the myocardium. In a normal person they found the following percentages: Pulse-pressure, 45 mm.

First phase	31.1 per cent.
Second phase	44.4 per cent.
Third phase	11.1 per cent.
Fourth phase	13.3 per cent.
	99.9 per cent.

C. S. : C. W. :: 55.5 : 44.4

Stone[5] has suggested the determination of a cardiac load and overload factor based on auscultatory blood-pressure determinations. He pointed out that in sixty-one normal persons with an average systolic pressure of 123 mm. and an average diastolic pressure of 80 mm., the pulse-pressure average was 40 mm.

"The amount of energy expended, therefore, to maintain the circulation in excess of that required to open the aortic valves and overcome the resisting pressure of 80, was 40. The normal load may, therefore, be considered to be $\frac{40}{80}$ or 50 per cent. of the diastolic pressure."

He has shown that in fourteen cases of decompensated myocardial disease the load was 76 per cent., an overload of 26 per cent. In fifty-one cases of arterial hypertension the load was 69 per cent., an overload of 19 per cent. He says that an overload factor of 50 per cent. indicates that there is impending danger of myocardial exhaustion.

In this paper I have compared the variations in the pulse-rate in the recumbent and in the erect posture, the cardiac efficiency factor of Tigerstedt, the percentage of the pulse-pressure formed by the second

2. Tornai: Ztschr. f. diät. u. physik. Therap., xiii, 809; abstr., Deutsch. med. Wchnschr., 1909, xxxv, 2287.

3. Fischer: Deutsch. med. Wchnschr., 1908, xxxiv, 1141.

4. Goodman and Howell: Univ. Penn. Med. Bull., 1910, xxiii, 469; Am. Jour. Med. Sc., 1911, cxlii, 334.

5. Stone, Willard, D.: The Clinical Significance of High and Low Pulse-Pressures, with Special Reference to Cardiac Load and Overload, Jour. Am. Med. Assn., 1913, lxi, 1256.

phase of the auscultatory blood-pressure reading, the C. S.: C. W. ratio of Goodman and Howell and the cardiac overload factor of Stone in ten fatal cases of cardiac and cardiorenal disease; in seven cases of compensated cardiac disease; in six cases of cardiac decompensation which subsequently had compensation restored; in eight cases of chronic interstitial nephritis in which the patients are still living, and in nine cases of various diseases in which the functional capacity of the myocardium was of importance in prognosis.

The blood-pressure observations were all made in the recumbent posture, with a 12 cm. cuff. In the tables, those marked * were made with a Tycos instrument, those marked † were made with a Riva Rocci and those marked § were made with a Stanton instrument. The auscultatory method was employed in every case. The first point, the appearance of the first tap, was recorded as the systolic pressure; and the fifth point, the disappearance of all sounds, was recorded as the diastolic pressure. In the tables — (minus) means that the observation was not made; + means that the formula could not be worked out.

In ten cases of cardiorenal disease fifty-three observations were made (Table 1). At many of these observations the difference in pulse-rate between the recumbent and the erect posture could not be obtained because the patients were confined to bed. At none at which the observation could be made was the increase excessive. It is significant that at two observations the pulse-rate decreased when the patient stood; in Case 424 there was a decrease of two beats; in Case 215 there was a decrease of six beats.

The cardiac efficiency factor was above 35 at forty-four observations. Once it was 35. In Case 105, a patient with chronic interstitial nephritis, pleural effusion, hypertrophy and dilatation of the heart, the factor was within normal limits three times and once it was much below normal, 19 per cent. The last record in this patient was made eight months before his death and the symptoms were more those of pleural effusion at the times at which I saw the patient than they were those of cardiac failure. In Case 180 likewise, although the patient died of uremia and the necropsy showed chronic parenchymatous nephritis, the symptomatology was that of indefinite abdominal disease (a chronic duodenal ulcer was found at necropsy) and the myocardium was not considered seriously impaired. The very high cardiac efficiency factor in Case 424 and in Case 511 is interesting in view of the fatal termination in two months in the one and within twenty-four hours in the other.

The second phase of the blood-pressure in these cases was below 40 per cent. of the pulse-pressure, when it could be worked out at every observation except four. In Case 215 the second observation,

TABLE 1.—Blood-Pressure Observations in Ten Fatal Cases of Cardiorenal Disease

No.	Date	Recumbent	Erect	C. E.	Second phase	C. S. : C. W.	Overload	Remarks
				%	%		%	
100*	2/ 5/12	—	—	42	3.5	+	23	Fibroid myocarditis.
	2/13/12	82	90[1]	49	14.0	+	46	[1]This observation of the pulse was made in the sitting posture.
	2/19/12	76	—	39	14.8	22.2 : 77.5	15	
	2/27/12	88	—	41	22.5	+	20	
	3/ 8/12	—	—	43	12.9	+	25	
	3/14/12	—	—	37	16.0	+	9	Tincture digitalis, 5 drops, nitroglycerin 1/100 grain four hours, begun 3/12/12.
	3/18/12	—	—	48	11.4	71.4 : 28.5	44	Tincture digitalis stopped. Patient died three weeks after this observation.
101*	5/ 2/12	54	—	38	17.6	+	11	Chronic parenchymatous nephritis. Cerebral thrombosis occurred to-day.
	5/ 3/12	52	—	34	9.6	+	2	Admitted to hospital.
	5/ 4/12	50	—	38	29.4	+	11	
	5/10/12	44	—	44	+	+	30	
	5/17/12	61	69[1]	47	30.0	+	38	[1]This observation of the pulse was made in the sitting posture.
	6/ 8/12	84	88	42	37.5	+	22	Improved sufficiently to leave hospital.
	6/15/12	84	86	36	31.4	+	8	The patient died twenty-three days after this observation was made.
105*	2/20/12	92	—	30	+	+	−7	Chronic interstitial nephritis.
	2/28/12	100	—	19	21	+	−26	
	7/13/12	84[1]	88	27	52.6	+	−12	[1]This observation of the pulse was made in the sitting posture.
	8/11/12	106	—	26	+	+	−15	The patient died eight months later.
180	8/25/12*	82	82	29	22.7	+	−8	Chronic parenchymatous nephritis.
	9/16/12†	84	—	31	13.6	+	−6	After three weeks hospital treatment.
	9/20/12†	94	100	37	52.9	76.4 : 23.4	10	Feeling well.
	6/ 6/13†	84	98	29	56.8	81.8 : 18.0	−9	Abdominal pain, nausea and vomiting and vertigo.
	8/15/13†	88	98	30	34.2	44.7 : 55.2	−6	Edema of the ankles, suborbital puffiness, tingling in fingers. Died seven months later.
215†	11/19/12	82	76	42	29.0	58.0 : 41.7	24	Angina pectoris.
	11/29/12	70	72	35	57.1	67.3 : 32.6	4	After four brine baths 98 F. Death about four weeks later.
220*	11/ 4/12	122	—	44	9.4	71.6 : 28.2	30	Mitral regurgitation.
	12/13/12	110	—	39	+	+	14	The patient died the next day.
229	1/ 8/13*	86	—	47	30.0	+	40	Chronic interstitial nephritis.
	1/10/13*	78	—	45	39.0	82.9 : 17.0	32	Patient in bed improving under treatment.
	1/15/13*	80	—	41	38.8	49.9 : 49.9	22	
	2/ 3/13*	84	—	50	13.0	86.9 : 12.19	52	Patient doing well.
	3/ 3/13*	72	—	49	20.4	+	48	Patient up and about, feeling well.
	3/20/13*	—	—	50	7.0	85.9 : 13.9	53	Before a brine bath.
	4/11/13*	—	—	49	9.0	+	46	After a brine bath.
	4/21/13*	78	—	45	20.4	79.5 : 20.3	33	
	5/ 1/13*	78	—	44	15.2	28.2 : 71.7	29	The brine baths do not agree with her; feels exhausted and does not sleep well.

In this and the following tables the observations made with the Tycos instrument are marked *, those with the Riva Rocci †, and those with the Stanton instrument §. The minus sign means that the observation was not made. The plus sign means that the formula could not be worked out.

TABLE 1.—(*Continued*)

No.	Date	Recumbent	Erect	C. E.	Second phase	C. S. : C. W.	Overload	Remarks
				%	%		%	
229	10/ 1/13†	82	—	52	12.0	87 : 13	61	The patient is not feeling well.
	11/29/13†	76	—	51	5.2	20.9 : 78.8	55	
	12/17/13†	86	86	48	23.7	90.7 : 9.2	42	Nausea.
	1/11/14*	78	—	41	16.6	+	22	Fairly well.
	1/31/14*	—	—	43	+	+	26	Beginning of last illness. Renal dyspnea, nausea and vomiting.
	2/ 5/14*	82	—	46	25.5	85.9 : 13.8	36	Pulmonary edema.
	2/12/14*	80	—	42	2.4	+	24	Temporary improvement.
	3/18/14*	82	—	39	20.5	+	15	Patient not so well. Death one week later.
414*	11/11/13	100	—	48	39.2	+	42	Auricular fibrillation.
	12/ 1/13	92	—	36	2.9	+	6	Nephritis.
	12/ 4/13	76	—	49	+	+	48	
	12/ 8/13	74	—	51	+	+	58	
	12/13/13	86	—	48	+	+	35	
	12/14/13	80	—	45	33.3	+	31	Cerebral thrombus.
	1/ 7/14	70	—	42	35.0	+	22	Some improvement in symptoms. The patient died about one month later.
424†	11/24/13	90	88	58	+	+	88	Mitral regurgitation. The patient died two months later.
511*	4/11/14	92	—	72	18.7	81.2 : 18.7	216	Uremia. The patient died the next morning.

which gave a percentage of 57.1, was made during a temporary improvement in the patient's condition.

The C. S.: C. W. ratio could be worked out at only twenty of these observations. The C. S. was greater than the C. W. factor at fifteen observations, and the two were equal once. At four observations the C. W. factor was greater than the C. S. factor. In the majority of the cases an absent point in the auscultatory blood-pressure determination makes it impossible to work out this proportion.

The cardiac overload factor was demonstrable in all cases except Case 105 and Case 108. In these the cardiac load was below 50 and gave a negative overload factor. In both of these cases the pulse-pressure was low. In Case 424 the overload amounted to 88 per cent.; in Case 511 to 216 per cent.

In seven compensated heart cases (Table 2) thirty-nine observations were made. In none was it possible to say that active decompensation was present. In Case 15 the chief complaint was weakness; in Case 127 it was a sensation of being tired; in Case 129 nervousness; in Case 176, weakness; in Case 275, rapid pulse; in Case 277, retrosternal pain; in Case 419, dyspnea.

TABLE 2.—Compensated Heart Cases

No.	Date	Recumbent	Erect	C. E.	Second phase	C. S. : C. W.	Overload	Remarks
				%	%		%	
15§	1/10/11	—	—	40	52.2	+	18	Parenchymatous myocarditis.
	1/12/11	—	—	34	+	+	6	Carbonated brine baths being given.
	1/14/11	—	—	44	63.2	71.3 : 28.5	31	
	1/16/11	—	—	52	28.3	36.9 : 46.6	59	
	1/18/11	—	—	45	8.5	+	32	
	1/20/11	—	—	39	26.1	73.7 : 26.1	15	Carbonated brine baths finished.
	1/21/11	68	90	46	29.0	43.5 : 56.3	37	Resistance exercises begun.
	2/13/11	—	—	56	10.9	51.5 : 48.4	78	
	2/20/11	—	—	50	48.2	85.7 : 14.2	53	
	2/27/11	—	—	43	46.9	69.3 : 30.5	35	
	3/ 6/11	—	—	50	46.2	+	51	
	3/13/11	—	—	40	44.4	55.5 : 44.4	18	Resistance exercises finished.
127	4/18/12*	96	104	31	26	+	—4	Mitral regurgitation.
	5/11/12*	74	—	38	32	84 : 16	12	During an attack of acute bronchitis.
	10/31/12†	80	90	24	56.6	+	—19	Digitalis 10 drops p. c.
	11/ 7/13†	72	80	36	43.7	62.4 : 37.4	8	
	11/14/13†	90	—	38	30.7	49.9 : 49.9	12	
129	4/23/12*	80	90	43	23.3	83.3 : 6.6	26	Mitral regurgitation.
	5/23/12*	90	100	46	30.4	+	0	
	2/15/13†	78	100	44	31.0	65.3 : 34.3	30	
	9/ 8/13†	88	108	37	55.5	+	10	
176	1/13/11§	76	90	43	28.3	62.2 : 37.7	31	Parenchymatous myocarditis.
	1/27/11§	70	80	39	27.9	55.8 : 44.1	15	
	2/10/11§	84	86	40	22.7	61.3 : 38.5	18	
	2/16/11§	70	82	41	22.9	+	19	After a course of carbonated brine baths.
	8/11/12*	64	78	40	18.1	+	16	
	8/13/13*	72	90	36	48.5	68.5 : 31.3	8	
227†	3/10/13	86	108	42	17.6	74.0 : 25.8	44	Angina pectoris.
	1/28/14	94	110	40	+	+	16	In the interval the patient had had a cerebral embolism.
275	13/ 5/13*	72	92	35	+	+	—8	Parenchymatous myocarditis.
	3/20/13*	68	—	35	+	+	—8	Carbonated brine baths begun.
	3/30/13*	—	—	39	30	72 : 28	14	
	4/ 4/13†	92	114	23	50	75 : 24.6	—20	
	4/12/14†	90	106	21	43.4	+	—19	
	4/15/14†	106	120	22	26.0	+	—21	Carbonated brine baths finished.
	4/22/14†	106	116	28	23.3	49.9 : 49.9	—10	
419†	11/20/13	100	114	30	+	+	—8	Mitral obstruction.
	12/ 9/13	96	—	24	+	+	—18	Digitalis begun.
	1/10/14	92	98	37	+	+	9	

In Case 15 the cardiac efficiency factor was above 35 per cent. at all observations except one. The second phase, however, was above 40 per cent. at all observations except five. When the C. S.: C. W. ratio could be worked out it was on the side of C. S. seven times and on the side of C. W. once. The cardiac overload was above 50 per cent. four times and below 50 per cent. eight times.

In Case 127 the cardiac efficiency factor was never much above or below the normal ratio, from 25 per cent. to 35 per cent. The second phase was below 40 per cent. at three out of five observations. The C. S. factor was above the C. W. at two observations at which the ratio could be worked out, and the two were equal at the other observation. There was no overload at two observations and at the other three the overload was insignificant.

In Case 129 the cardiac efficiency factor was high at three out of four observations. The second phase was below 40 per cent. at three observations. At two observations at which the C. S. : C. W. ratio could be worked out the C. S. factor was the higher. The overload was insignificant.

In Case 176 the cardiac efficiency factor was slightly in excess. The second phase was below 40 per cent. at all observations except the last. The C. S.: C. W. ratio could be worked out at four out of six observations, and the C. S. factor was always greater. The cardiac overload was not great.

In Case 275 seven observations were made. The cardiac efficiency factor was always in the neighborhood of normal limits. The second phase was above 40 per cent. at two only. At three only could the C. S.: C. W. ratio be determined; at two of these the C. S. was greater than the C. W.; at the other the two factors were equal. The overload factor was a minus quantity at all observations except one, at which it was insignificant.

In Case 277 the cardiac efficiency factor was above the normal. The second phase was low at the observation at which it could be worked out. The C. S.: C. W. ratio was in favor of the C. S. factor. The overload was 44 per cent. at the first and 16 per cent. at the second observation.

In Case 419 the cardiac efficiency factor was about normal. The second phase and the C. S.: C. W. ratio could not be worked out. There was no overload factor except an unimportant one at the last observation (9 per cent.).

In six cases (Table 3) compensation was lost at the time the patients were first seen, but was restored after treatment so that they could resume their usual occupations. Three of the patients suffered

TABLE 3.—Cases in Which Compensation Was at First Lost to Be Restored Subsequently

No.	Date	Recumbent	Erect	C. E.	Second phase	C. S. : C. W.	Overload	Remarks
				%	%		%	
147a†	10/ 2/13	84	98	24	+	+	−19	Mitral regurgitation. Decompensated. Ambulant.
	11/ 4/13	76	92	36	+	+	8	Compensated.
	1/ 8/14	84	—	46	+	+	36	Partially decompensated.
	4/ 4/14	66	74	33	+	+	0	Compensated
191	9/28/12†	68	86	45	15.7	70 : 29.8	33	Mitral regurgitation. Compensated.
	12/ 3/12*	64	70	49	+	+	46	Acute dilation.
	12/ 6/12*	60	—	40	20.0	40 : 60	17	In bed under treatment improving.
	12/17/12†	70	90	48	31.0	68.9 : 30.9	42	Up and about the house. Compensation restored.
	12/26/12†	76	96	52	29.8	74.5 : 25.3	61	After three carbonated brine baths.
	1/ 3/13†	86	96	45	26.8	75.3 : 24.8	32	After six carbonated brine baths.
	1/10/13†	68	84	49	22.0	55.8 : 43.8	48	After nine carbonated brine baths.
	1/17/13†	70	86	50	30.6	72.5 : 27.3	48	After twelve carbonated brine baths.
	2/ 6/13†	72	94	52	45.4	60.5 : 39.3	60	After eighteen carbonated brine baths.
	4/10/13†	72	84	44	45.0	64.6 : 35.2	29	Just before going to Bad Nauheim.
	9/10/13†	70	80	52	46.1	76.8 : 22.9	58	Two months after returning from Bad Nauheim.
	1/10/14†	86	114	45	+	+	29	After carbonated brine baths.
	3/12/14†	66	—	51	30.6	74.1 : 25.7	55	
291	3/24/13*	102	—	88	9.8	64.7 : 35.1	178	Aortic regurgitation. Marked decompensation.
	6/ 5/13*	112	—	58	+	+	90	Improving.
	10/ 9/13*	86	—	71	16	86 : 14	200	Compensated
	11/ 6/13†	74	80	74	20.6	32.0 : 67.7	240	
	12/16/13†	74	80	80	15.2	80.9 : 18.9	370	
373†	8/27/13	80	86	88	13.7	+	723	Aortic regurgitation. Decompensated.
	9/ 1/13	68	76	84	4.5	22.6 : 77.2	500	Some improvement.
404	10/19/13*	82	90	40	15.3	19.1 : 80.7	16	Mitral regurgitation. Partially decompensated.
	10/20/13*	84	—	34	+	+	2	Twenty-four hours rest in bed.
	10/22/13*	78	—	48	+	+	26	
	10/28/13*	82	—	50	19.3	70.9 : 28.9	50	
	11/ 6/13*	72	—	44	23.3	33.3 : 66.6	31	Patient allowed to sit up. Compensated.
	11/25/13*	70	80	46	15.6	59.1 : 40.6	36	
	12/ 4/13*	74	—	39	34.6	38.4 : 61.5	15	
	12/24/13*	84	—	42	32.0	80 : 20	23	
	1/ 8/14*	78	—	49	34.3	65.5 : 34.3	46	
	2/20/14†	70	—	45	25.9	66.6 : 33.3	31	
	3/27/14†	76	82	45	13.1	86.8 : 13.0	32	
456*	1/ 5/14	88	—	39	+	+	14	Auricular fibrillation. Decompensated.
	1/27/14	84	—	30	91	+	−7	Compensation reestablished.

from mitral regurgitation, two from aortic regurgitation and one from auricular fibrillation.

In Case 147a the variation in the pulse-rate between the recumbent and the erect posture was 14, 16 and 8 beats at three observations. The cardiac efficiency was below 25 per cent. when he was first seen; was 36 per cent. at the second observation when compensation was good; 46 per cent. at the third observation when compensation was again partially lost, and 33 per cent. at the fourth observation, when compensation had again been restored. The second phase and the C. S.: C. W. ratio could not be determined. The cardiac overload was 19 per cent. negative at the first observation during decompensation; 8 per cent. at the second observation when compensation was restored; 36 per cent. at the third observation when compensation was again lost, and 0 at the fourth observation when compensation was restored.

In Case 191 the pulse increase between the recumbent and the erect posture was over 10 beats at eight observations, both during an attack of acute dilatation and after compensation had been restored. The cardiac efficiency factor was above 35 per cent. at every observation. The second phase rose during the course of carbonated brine baths from 15.7 per cent. to 45.0 per cent.; the C. S.: C. W. ratio fluctuated, and the overload varied, being 46 per cent. just after the acute dilatation occurred and increasing to 61 per cent. and 60 per cent. at two observations during the course of carbonated brine baths.

In Case 404 the observations on the pulse-rate in the recumbent and the erect postures were not systematically made. The cardiac efficiency factor fell from 40 per cent. to 34 per cent. after twenty-four hours in bed, but subsequently rose and was 39 per cent. or over at all the subsequent observations. The second phase formed 15.3 per cent. of the pulse-pressure at the first observation, but improved and at one time formed 34.6 per cent. of the pulse-pressure. The C. S.: C. W. ratio was at first 19.1 : 80.7 and subsequently varied, but the C. S. factor was greater than the C. W. factor at six out of eight observations. The cardiac overload was never excessive, the highest being 50 per cent. nine days before the patient was allowed to get up.

In the cases of aortic regurgitation the cardiac efficiency factor was very high both during decompensation and during compensation. The second phase was low at all times, the C. S.: C. W. ratio varied and the cardiac overload was excessive.

In the case of auricular fibrillation the cardiac efficiency factor was 39 per cent. during decompensation and 30 per cent. during compensation. The phases could not be determined during decompensation; but after compensation had been established the second phase formed 91 per cent. of the pulse-pressure. The cardiac overload factor was

TABLE 4.—Cases of Chronic Nephritis

No.	Date	Recumbent	Erect	C. E.	Second phase	C. S. : C. W.	Overload	Remarks
				%	%		%	
104	2/19/12*	68	76	36	11.5	+	6	Chronic nephritis. Arhythmia.
	2/29/12*	76	—	54	7.1	+	70	
	3/ 7/12*	78	—	40	+	+	47	
	3/18/12*	76	88	44	+	+	33	
	4/24/12*	60	64	57	17.5	+	83	
	5/ 8/12*	70	72	55	11.1	68.8 : 31.0	78	
	5/29/12*	74	98	42	10.3	+	24	
	6/26/12*	74	84	33	+	+	1	Arhythmia cleared up. Feeling well.
	8/13/12*	68	78	36	13.3	+	7	
	9/15/12†	80	88	33	+	+	1	
	12/30/12†	82	94	29	25.5	46.4 : 53.4	−7	
	10/22/13†	86	92	41	26.3	+	21	Return of arhythmia.
154*	6/24/12	74	88	41	22.5	+	21	Chronic nephritis.
	6/30/12	74	88	42	16.2	+	24	
	7/ 8/12	82	96	40	27.7	+	16	
	7/15/12	74	78	40	19.0	+	16	
	7/22/12	72	74	38	31.7	+	13	Electric light baths finished.
	8/ 5/12	—	—	42	31.2	+	25	
	9/ 2/12	—	—	38	23.8	+	12	
268†	2/28/12	74	80	40	19.6	74.1 : 25.6	17	Chronic nephritis.
	4/ 8/13	68	72	39	21.3	29.4 : 70.4	14	
	4/22/13	78	86	39	22.0	52 : 48	−7	
	6/ 2/13	72	78	39	48.4	64 : 35.8	14	
	6/30/13	90	96	38	29.5	90.4 : 9.3	10	
	7/31/13	74	—	34	25.0	82.6 : 17.2	2	
	8/28/13	—	—	37	16.6	33.2 : 66.6	10	
	11/11/13	64	68	38	+	+	16	Electric light baths begun.
	1/ 4/14	72	76	34	+	+	3	
	2/28/14	70	74	38	23.7	88.1 : 11.7	11	
	3/19/14	60	68	28	68.5	+	−12	
	4/ 9/14	68	74	33	47.5	70 : 30	0	
431†	11/24/13	62	72	55	28.7	91.2 : 8.7	73	Chronic nephritis.
	12/ 6/13	70	78	54	41.6	83.2 : 16.6	70	
	12/22/13	70	92	52	34.8	95.4 : 4.5	61	Electric light baths finished.
478	2/18/14†	66	74	44	12.0	78.6 : 21.2	24	Chronic nephritis.
	3/18/14†	78	84	52	19.7	61.9 : 38.0	59	
	3/29/14*	72	—	41	+	+	21	Attack of auricular fibrillation. In bed.
	3/30/14*	72	—	36	+	+	6	
	3/31/14*	104	—	42	+	+	24	

TABLE 4.—(*Continued*)

No.	Date	Recumbent	Erect	C. E.	Second phase	C. S. : C. W.	Overload	Remarks
				%	%		%	
479	2/21/14†	100	—	44	+	+	29	Chronic nephritis. Hyperthyroidism.
	2/28/14*	—	—	36	36.8	86.8 : 13.0	8	In bed one week.
	3/ 9/14*	—	—	42	6.9	+	22	Hospital. Hot brine baths and blanket packs.
	3/12/14*	80	—	39	15.3	+	15	
	3/16/14*	74	—	42	+	+	25	
	3/23/14*	90	—	41	31.7	+	15	Returned from hospital.
	3/28/14*	90	—	36	+	+	6	
	4/ 8/14†	96	96	44	3.6	+	31	
	4/22/14†	108	120	41	6.5	85.4 : 14.4	19	

14 per cent. during decompensation and was 7 per cent. negative after compensation had been regained.

We must not forget in the interpretation of these results that after compensation is restored these hearts are diseased. Valvular defect and the compensatory hypertrophy still make the heart an abnormal organ.

In six cases of chronic nephritis forty-eight observations were made (Table 4). The pulse-rate in the erect posture was more than ten beats above that in the recumbent posture at eight observations. The cardiac efficiency factor was above 35 per cent. at forty observations. The second phase formed less than 40 per cent. of the pulse-pressure at thirty-two. The C. S.: C. W. ratio, when it could be worked out, showed the C. S. factor in excess of the C. W. factor at fifteen observations, and a C. W. factor greater than the C. S. factor at three observations. The overload varied, but was above 50 per cent. at seven observations. The load was below the normal of 50 per cent. at three observations.

In Case 154 and Case 268, both of which showed a small overload, the symptoms were never urgent during the period of observation.

In general, it seems safe to conclude that all of these factors may be looked on as indicating to some extent the ability of the myocardium to perform its work. The variation in the pulse-rate between the recumbent and the erect posture is perhaps the least reliable.

A cardiac efficiency factor above 35 per cent., a second phase forming less than 40 per cent. of the pulse-pressure, and a cardiac overload approaching 50 per cent. or more than 50 per cent. may be looked on as pointing to myocardial insufficiency. The C. S. : C. W. ratio in many

cases cannot be worked out because the fourth point cannot be determined; but when it can be worked out a C. W. factor in excess of the C. S. factor points to serious myocardial disturbance.

I have selected nine cases from my records for the purpose of illustrating the way these factors work out on patients who clinically cannot be classed as cardiacs or as nephritics.

CASE 125.—Man, aged 54 years when first seen April 7, 1912. Chief complaint, nervousness and irritability. Physical examination revealed overweight, weak heart muscle, low blood-pressure, irritable pulse. Blood examination revealed chloro-anemia, lymphocytosis. May 3, 1913, a diagnosis of acute dilation of the heart was made on account of an increase in the oblique diameter of cardiac dulness from 18 cm., Oct. 7, 1912, to 22 cm., muffled heart sounds and an impure systolic sound with cyanosis, palpable liver edge, a drop of the systolic blood-pressure from 100 mm. to 95 mm. and a sensation of precordial distress. In August, 1913, he had an attack of acute dyspeptic diarrhea after eating clams. In April, 1914, he had acute bronchitis.

TABLE 5.—OBSERVATIONS IN CASE 125

Date	Recumbent	Erect	C. E.	Second phase	C. S. : C. W.	Overload	Remarks
			%	%		%	
4/ 7/12*	66	86	26	+	+	−14	
7/14/12*	60	70	35	36.8	+	4	
10/ 7/12†	66	72	30	28.3	+	−8	Clinically acute dilatation of the heart.
5/ 3/13†	72	90	30	62.0	72.3 : 27.4	−7	
5/23/13†	58	68	35	42.8	57.0 : 42.8	4	
5/27/13†	64	74	32	46.8	+	−2	
7/20/13†	56	64	31	40.7	+	−5	
9/ 1/13†	58	70	34	+	+	1	Tincture digitalis, 6 minims p. c.
4/12/14†	58	..	33	+	+	0	Digitalis stopped.

A study of the factors set forth in tabular form would seem to show that this myocardium was competent.

CASE 162.—Man, aged 37 years when first seen, July 10, 1912. The chief complaint was that a life insurance examiner had rejected him on account of pulmonary tuberculosis. Physical examination revealed healed pulmonary tuberculosis, slight hypertrophy of the heart, arhythmia, gastrectasia, high blood-pressure. After a month spent in the Adirondack Mountains, at Fourth Lake, his symptoms had markedly improved, but the arhythmia persisted. After taking sodium iodid for two months the arhythmia was still present. A polygraphic tracing showed the irregularity to be due to ventricular extrasystoles. Later the arhythmia temporarily disappeared. In March, 1913, he had an attack of spasmodic torticollis. In August, September and October, 1913, he had two attacks of acute constipation, and two attacks of acute epigastric pain. A bismuth roentgenogram, made by Dr. M. B. Palmer, showed no organic stomach disturbance. The circulatory study would indicate a competent myocardium.

CASE 203.—Man, aged 42 years when first seen, Oct. 30, 1912. Chief complaint, cardiac arhythmia for sixteen or seventeen years. Physical examination revealed scoliosis, arhythmia, high blood-pressure, rapid pulse. Urine: Specific gravity 1.029 to 1.021; albumin, trace at one examination in five; a few hyaline casts twice, a few epithelial casts twice, no casts once. Eye-grounds negative after an attack of acute dyspeptic diarrhea in March, 1914 (examination made by Dr. A. C. Snell). At the time a polygraphic tracing was made the pulse was regular. The increase in heart rate between the erect and the recumbent postures, I ascribe to nervous influence. The patient had been badly scared by serious prognoses given him about his heart. The study of the circulation would indicate a competent myocardium.

TABLE 6.—OBSERVATIONS IN CASE 162

Date	Recumbent	Erect	C. E.	Second phase	C. S. : C. W.	Overload
			%	%		%
7/10/12*	58	74	38	44.4	85.1 : 14.8	12
8/19/12*	66	82	39	26.8	+	15
11/19/12†	72	78	31	33.3	69.1 : 30.6	—4
12/17/12†	70	78	25	57.5	87.8 : 12.0	—15
2/19/13†	70	82	44	50	63.4 : 36.4	30
3/21/13†	66	74	21	31.8	63.6 : 36.3	—23
9/29/13†	74	90	33	37.5	62.5 : 37.5	0
10/18/13†	76	—	31	42.9	59.9 : 39.9	—4

TABLE 7.—OBSERVATIONS IN CASE 203

Date	Recumbent	Erect	C. E.	Second phase	C. S. : C. W.	Overload	Remarks
			%	%		%	
10/30/12†	72	96	35	35	+	5	Electric light baths and massage.
11/ 8/12†	82	88	30	26.5	77.5 : 22.4	—6	
11/22/12†	78	80	27	37.5	+	—12	
11/29/12†	76	96	26	37.8	64.8 : 35.1	—15	Electric light baths finished.
12/28/12†	74	88	27	59.5	+	—12	
2/ 8/13†	78	88	33	65.2	+	1	
3/ 8/13†	84	100	30	63.6	79.5 : 20.3	—6	
5/ 2/13†	78	90	33	33.3	66.5 : 33.2	—1	
11/18/13†	88	—	27	11.9	+	—12	
3/ 4/14*	—	—	28	50.0	+	—18	Acute dyspeptic diarrhea.
3/15/14†	90	..	27	13.3	+	—13	

CASE 233.—Man, aged 57 years. Chief complaint three persistent colds in six weeks. Physical examination revealed acute nasopharyngitis, pulmonary emphysema, palpable liver edge. The examination of the heart gave the following results: "P. M. I. fifth interspace, 10.5 cm. to the left of the midsternal line. Dulness, third rib, fifth interspace, 2.5 cm. to the right of the midsternal

line, 11 cm. to the left of the midsternal line. Oblique diameter of cardiac dulness, 17.5 cm. No murmurs. The aortic diastolic sound is louder than the pulmonary diastolic sound. The muscular quality of the systolic sound is good. Blood pressure, recumbent, Riva Rocci instrument:

First point	157	First phase	12.2 per cent.
Second point	150	Second phase	26.3 per cent.
Third point	135	Third phase	52.6 per cent.
Fourth point	105	Fourth phase	8.7 per cent.
Fifth point	100	C. S. : C. W. :: 78.9 : 20.9	

"Pulse-pressure, 57; cardiac efficiency, 35 per cent.; cardiac load, 57 per cent.; overload, 7 per cent."

The cardiac symptoms were dyspnea and palpitation of the heart on exertion. The cardiac condition was considered at the time of the examination to be a part of an obesity; the patient was 5 feet, 9 inches tall and weighed 180 pounds, 15 ounces. The myocardium was thought to be competent. "The cardiac condition is thought to be due to the increased deposit of fat in the epicardium and not to degenerative changes in the muscle fibers."

CASE 299.—Woman, aged 40 years. Chief complaint, irregular heart. Physical examination revealed palpable liver, arhythmia. "Heart: P. M. I., not obtainable. Dulness, third rib, fifth interspace, 3 cm. to the right of the midsternal line, 10.8 cm. to the left of the midsternal line. Oblique diameter of cardiac dulness, 16 cm. The sounds at the apex are clear. The sounds at the base are clear. The pulmonary diastolic sound is louder than the aortic diastolic sound. The muscular quality of the systolic sound is good." Blood-pressure, recumbent, Riva Rocci instrument:

First point	124	First phase	10.2 per cent.
Second point	119	Second phase	38.7 per cent.
Third point	100	Third phase	40.8 per cent.
Fourth point	80	Fourth phase	10.2 per cent.
Fifth point	75	C. S. : C. W. :: 79.5 : 20.4	

Pulse-pressure, 49; cardiac efficiency, 39 per cent.; cardiac load, 61 per cent.; overload, 11 per cent. The urine contained neither albumin nor casts. The blood showed a polycythemia, low color index, high lymphocyte percentage (26.8 per cent.), and eosinophilia (8.4 per cent.). A polygraphic tracing gave a distinct pulsus bigeminus. The analysis of the functional tests would leave some doubt concerning the capacity of the myocardium.

CASE 309.—Woman, aged 47 years. Chief complaint, attacks of palpitation of the heart. Physical examination revealed palpable thyroid body, hypertrophy of the heart, gallop rhythm, palpable and tender liver edge, gastrectasia, high blood-pressure. The urine contained a trace of albumin and a few hyaline casts at the first examination. Gastric analysis, after Ewald test breakfast: Amount removed, 45 c.c.; free hydrochloric acid, 28; total acidity, 48; lactic acid, negative; occult blood, negative. Microscopic large amount of partly digested food not finely divided. (Examination made by Dr. C. C. Sutter.) Bismuth roentgenogram showed cowhorn type of stomach, with the greater curvature just below the umbilicus. (Examination made by Dr. M. B. Palmer.)

At the first examination there was definite evidence of disturbance of myocardial function, which improved while under treatment directed toward the dilated stomach. After the patient had omitted her treatment for about ten days the evidence of myocardial disturbance returned.

CASE 327.—Man, aged 45 years. Chief complaint pain in right side of chest. Physical examination revealed palpable liver edge, low blood-pressure, slow pulse. Urine, no albumin, one hyaline cast seen. Increase in pulse-rate between the recumbent and the erect posture, 10 beats; cardiac efficiency within normal limits; second phase below normal; impossible to obtain C. S : C. W. ratio.

No overload. It is possible that the low second phase and the impossibility of working out the C. S. : C. W. ratio on account of the absence of the fourth point may point to myocardial weakness; but there was no clinical evidence of it.

Case 405.—Man, aged 49 years. This patient had been refused the renewal of a life-insurance policy because his systolic blood-pressure was high (154 mm.). Physical examination showed a slight increase in the oblique diameter of cardiac dulness (17 cm.), palpable liver edge, slow pulse and an increase of twenty beats between the recumbent and the upright posture. Urine examination. Specific gravity, 1.030. No albumin, no casts. The second phase, 12.7 per cent. and the C. S. : C. W. ratio of 32.7 to 67.2 in favor of myocardial weakness are balanced by a cardiac efficiency of 35 per cent. and an overload of only 5 per cent.

TABLE 8.—Observations in Six Cases

No.	Date	Sex	Age	Recumbent	Erect	C. E.	Second phase	C. S. : C. W.	Overload	Remarks
						%	%		%	
233†	12/23/12	M	57	88	94	35	26.3	78.9 : 20.9	7	Fat heart.
296†	3/17/13	F	40	54	—	39	38.7	79.5 : 20.4	15	Hyperthyroidism
	11/11/13	..	..	—	—	38	51.0	+	11	
309*	4/22/13	F	47	100	—	41	35.0	64.7 : 35.1	21	Gastrectasia.
	5/22/13	..	..	84	114	31	31.8	49.9 : 49.9	—4	
	6/20/13	..	..	86	—	22	44.0	60 : 40	—22	
	6/23/13	..	..	86	—	22	36.3	73.6 : 26.4	—2	
	7/22/13	..	..	84	100	22	21.7	43.4 : 56.4	—2	
	9/30/13	..	..	90	—	29	10.3	+	14	
227†	8/14/13	M	45	56	66	28	24.1	+	—14	No definite organic lesion.
405†	10/23/13	M	49	66	86	35	12.7	32.7 : 67.2	5	Hypertrophy of the heart.
409†	11/ 8/13	M	54	100	114	37	18.6	74.5 : 25.3	9	Electric light baths begun.
	11/20/13	..	..	72	—	40	26.7	73.1 : 25.8	18	
	12/10/13	..	..	72	84	45	20.5	59.6 : 40.2	24	Electric light baths finished.

Case 409.—Man, aged 54 years. Chief complaint, abdominal pain. Physical examination revealed slight exophthalmos, enlarged thyroid body, beginning pulmonary emphysema, increased area of cardiac dulness, palpable liver edge, high blood-pressure, and rapid pulse. The patient complained of right-sided abdominal pain, which was relieved by a cathartic, and some dyspnea and palpitation of the heart on exertion, which he ascribed to his weight. Although he was apparently in perfect health, the physical examination showed definite but early changes in thyroid body, heart, lungs and liver. He weighed 203¼ pounds, an excess of 26 pounds for his height, 5 feet, 11½ inches. The urine had a specific gravity of 1.011 and 1.012. Neither albumin nor glucose was present. There was a slight excess of indican. The microscope showed pus, round epithelium and phosphates.

The cardiac efficiency factor and the second phase would point to some myocardial deficiency, although the C. S. : C. W. ratio and the overload factor would not indicate such weakness. A course of electric light baths was followed by subjective improvement: that is, while he was not complaining before the baths were taken, he felt better after they had been finished and then realized that he had not been quite up to the mark. The cardiac efficiency

factor, the second phase, the C. S. : C. W. ratio and the overload then all pointed to myocardial defect. Three months later the urine had a specific gravity of from 1.026 to 1.028 and contained glucose. After two weeks on a low carbohydrate diet the total quantity of urine was 2,470 c.c.; specific gravity, 1.012; there was a trace of albumin by the Tsuchiya method; no glucose. Six weeks later the total quantity was 2,087 c.c.; specific gravity, 1.016; neither albumin nor glucose; no excess of indican.

CONCLUSIONS

It appears to me legitimate, from the study of the cases herein reported, to conclude that all four of these factors have some value in determining the efficiency of the myocardium. I am inclined to think at present that the cardiac efficiency factor of Tigerstedt, and the percentage of the pulse pressure formed by the second phase, are the most important. A cardiac efficiency factor of 40 per cent. or over would seem to point out distinct myocardial inefficiency. A second phase of 30 per cent. or under would seem to indicate the same condition.

The C. S.: C. W. ratio is less important, I think, because it so often cannot be determined; and again, because a small second phase is very frequently made up by a large third phase. On the other hand, a C. S.: C. W. ratio in which the C. W. factor is greater than the C. S. factor is indicative of disturbance of the myocardium, functional if not organic. I am inclined to think at present that the overload factor of Stone is indicative more of peripheral resistance than of myocardial weakness. A cardiac load below 50 per cent., as determined by this method, giving a negative overload may have some significance; but it will require further study to determine its nature.

THE THERAPEUTIC ACTION OF IODIN*

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Though iodin in the form of inorganic iodids or as organic compounds has been used for years, and is one of the most important drugs in the Pharmacopeia, little is known concerning its action in the body. This lack of knowledge applies particularly to its effect in causing the absorption of necrotic material such as is found in gummas.

The results obtained with the iodids have been variously ascribed to their influence in the general metabolism of the body; to their supposed action in causing a fall in blood-pressure; to a change in the viscosity of the blood; to a lymphocytosis; to an increase in the activity of the lymphatics, and to the oxidizing properties of the nascent iodin.

Binz[1] and Hinz[2] believed its action to be due to the oxidizing properties of the nascent iodin, which, according to Hinz, renders the blood-vessels more permeable and makes the leukocytes more active. Romberg[3] suggests that its action may be due to some change in the blood, and Müller and Inada[4] state that this change consists in an alteration of the viscosity. Determann,[5] however, denies that there is a change in the viscosity of the blood following the administration of iodids.

Various authors have ascribed the action of iodin to its property of causing a fall in blood-pressure, but Stockman and Charteris[6] state that there is no fall in blood-pressure when iodids are given. Lehndorf,[7] however, in a recent paper states that iodids do cause a fall of the blood-pressure, and believes that the lowered blood-pressure aids healing by permitting a better circulation of blood through the diseased area.

Much work has been done on the absorption, distribution and excretion of iodin; we shall, however, refer only briefly to this. All who have investigated the subject have found that the inorganic

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iodids are absorbed very rapidly, and in the main are excreted as inorganic compounds, while the organic compounds, especially those in which the iodin is combined with fatty acids, as in iodipin, are absorbed and excreted more slowly. According to Winternitz,[8] iodipin is absorbed from the intestinal tract as iodized fatty acids, and by oxidation of these the iodin is split off and is excreted principally in the form of inorganic iodids. Wells[9] concludes from his work that when iodipin is injected into the subcutaneous tissues it is carried in the blood chiefly as inorganic iodids. McLean[10] made a study of the distribution of iodin in the body of rabbits which had received several doses of potassium iodid, and found that the lipoid fractions of the tissues contained 32 per cent. and the water-soluble fraction 67 per cent. of the iodin. The extracted protein contained no iodin. The older view that iodin combines with the proteins of the body has been disproved by McLean and other observers. We believe we are justified in assuming that a large part of the iodin combines with the lipoids, as the work of McLean and Winternitz indicates that such organic compounds, whether given as such or formed in the body, are in turn readily oxidized, and the iodin excreted chiefly as inorganic compounds. Bröking[11] has shown that iodin administered as iodized fats or fatty acids is not excreted so rapidly as when given in the form of potassium iodid. This is to be expected, as absorption would be less rapid, and new compounds must be formed before it can be excreted, whereas potassium iodid is more readily absorbed and excreted as such.

Reference books on pharmacology and therapeutics afford but little information on the action of iodin. Forschheimer[12] states that iodin stimulates the activity of the lymphatics and increases the energy of the nutritive processes, and thus promotes the absorption of disease products. Schmiedeberg[13] states that iodin does not exert a specific action on any organ, but causes a change in metabolism and in nutritive processes in general.

In the present work we have confined our investigations of the action of iodin to its influence on the antitrypsin of the blood and tissues, as we believe that the antitrypsin is the most important factor in preventing the resolution of necrotic tissues such as are found in infarcts, and in the caseous areas in syphilis and tuberculosis.

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ANTITRYPSIN

In a recent publication[14] we reported that the ferment-inhibiting action of serum is due to the presence of compounds of the unsaturated fatty acids. The ease with which they can be extracted by chloroform or ether indicates that they are either free acids, or that they are combined with lipoids. The influence of chloroform on the antitrypsin of serum and the rapidity with which it acts is shown in Chart 1. In this experiment two volumes of chloroform were added to fresh serum and the mixture was placed in the incubator for one hour. During this time it was shaken thoroughly at short intervals. At fifteen-minute intervals some of the serum was removed and tested for its ferment-inhibiting properties. In separating the serum from the chloroform it is necessary to centrifuge at high speed for about five to ten minutes,

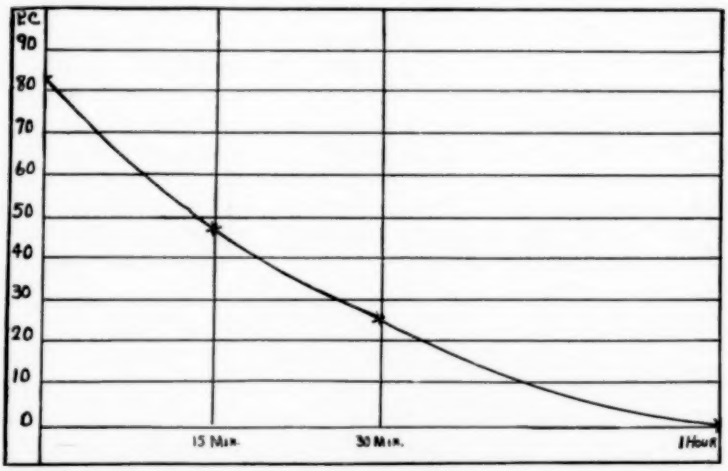

Chart 1.—Rate of removal of serum antitrypsin by chloroform extraction at 37 C. (98.6 F.).

and then to filter several times through coarse filter-paper until the serum is quite clear and all the chloroform evaporated. This experiment demonstrates that the ferment-inhibiting action of the serum is almost wholly lost after sixty minutes' incubation with chloroform.

That the inhibiting action is due to fatty acids is shown by the following experiment, the results of which are shown in Chart 2.

Ether was added to fresh dog-serum, and the mixture was allowed to stand at room temperature for two days. The ether was then removed, evaporated to dryness and the substance remaining saponified

14. Jobling, J., and Petersen, W.: Jour. Exper. Med., 1914, xix, 459.

by means of sodium alcoholate. After evaporating to dryness, the soaps were dissolved in water, the acids liberated in the usual manner, taken up in ether and resaponified. These soaps and some of the untreated serum were then tested to find out their ferment-inhibiting action.

The chart shows that the soaps prepared from the ether extract cause nearly as much inhibition as the untreated serum. Subsequent experiments showed that the chloroform and ether extracts lost their ferment-inhibiting action if they were first treated with iodin, which indicates that the active agents were the unsaturated fatty acids.

The demonstration that the antitryptic action of the blood and of tuberculous caseous matter is due to the presence of unsaturated fatty acids suggested to us the possibility that the action of iodin in the body

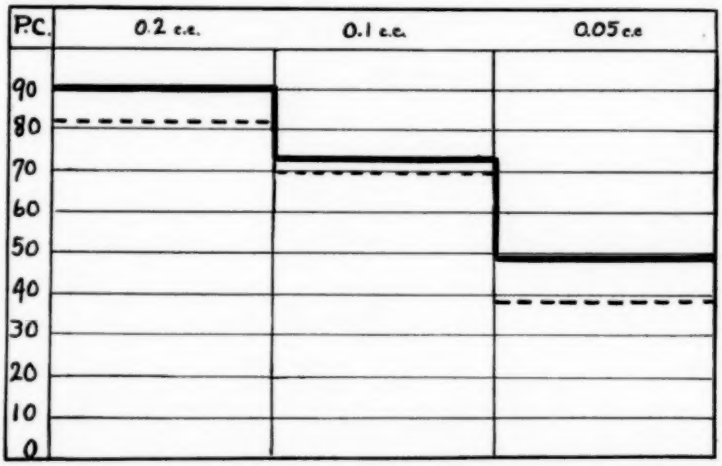

Chart 2.—Antitryptic effect of saponified ether extract of normal serum. Solid line, inhibition of normal serum; broken line, inhibition of saponified extract.

may be due to a combination with the fatty acids, thus causing a neutralization of the activity of these substances as ferment-inhibiting agents. If this supposition proved true, the neutralization of the activity of these agents should lower the antienzyme strength or the blood-tissues in general and permit the removal of dead tissues by autolysis.

The next experiment was made to determine the influence of potassium iodid on the antitrypsin of guinea-pig serum.

Fresh guinea-pig serum was mixed with potassium iodid in the proportion of 0.2 gm. of the iodid to 1 c.c. of the serum, and the mix-

ture placed in the incubator over night. Some of the untreated serum was used as a control. Chart 3 shows the results of this experiment.

The chart shows the great decrease in antitryptic strength of the serum after treatment with potassium iodid. Similar results were obtained when the serum was treated with hydrogen dioxid. The foregoing observations led us to study the antitryptic strength of the serum of patients to whom iodids were being given. It seemed probable, especially from the results obtained by McLean, that some of the iodin would combine with the unsaturated fatty acids of the body, and as a result lower the antitryptic strength of the serum and of the tissues in general. This decrease in antitrypsin would permit the ferments normally present in the necrotic areas to become active, and thus hasten autolysis.

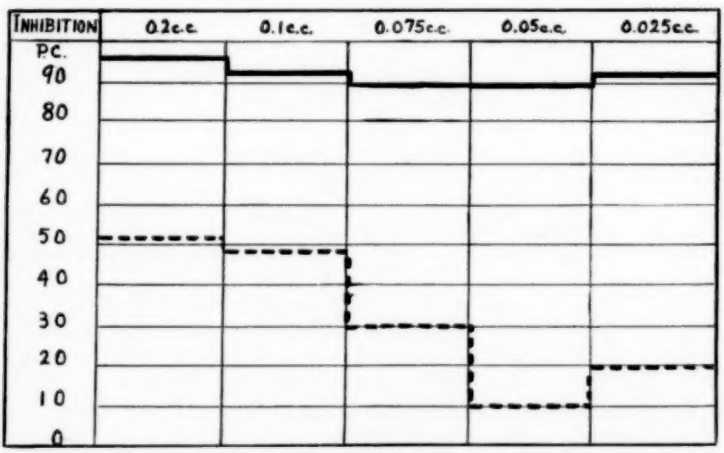

Chart 3.—Effect of potassium iodid on antitrypsin of guinea-pig serum. Solid line, normal serum; broken line, normal serum with potassium iodid incubated over night.

We are greatly indebted to Drs. J. Fordyce, W. McMurty and C. Sharpe for furnishing us with the clinical material used in this study, and also for regulating the dosage of iodids and determining the clinical condition of the patients while the work was progressing. Thirteen cases were studied, eleven of which were syphilitics. In each instance the blood was tested before iodids were given. The second test was made when the patient was receiving about 100 grains a day, and the third when he had reached the limit of tolerance. We were unable to carry out this plan in all cases, as the patients did not always follow directions.

In making the tests the trypsin was mixed with the various dilutions of serum and incubated thirty minutes. Two c.c. of a 1 per cent. casein solution was then added to each tube, and the mixtures were incubated one hour. The contents of the tubes were then acidified with a mixture containing 10 per cent. glacial acetic acid and 20 per cent. sodium chlorid and the tubes placed in boiling water for from five to ten minutes. The mixtures were then filtered through kaolin, and non-coagulable nitrogen was determined by the method recommended by Folin and Denis.[15] The results are given in percentage of total control digestion. The trypsin used in this work was prepared according to the method described in a previous paper,[16] and made into solution when required.

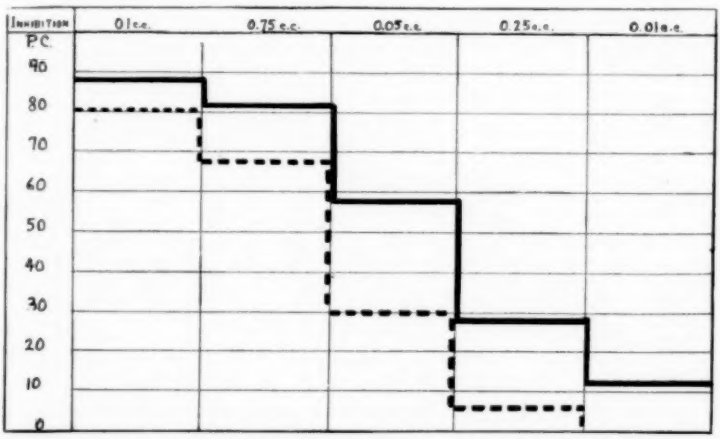

Chart 4.—Average of human cases on potassium iodid (110 gr.).

Chart 4 gives the average of the antitryptic strength of the serums of the thirteen cases before and after using iodids. The black line represents the strength of the serums before iodids were administered, and the dotted line the average strength of the serums when the patients were taking about 110 grains a day. The action of the iodids is best seen in the dilutions beginning with 0.05 c.c. of serum, though some effect is observed in the more concentrated solutions.

This series of cases is not large, but sufficiently so to show that iodids administered to human beings cause a very considerable reduction in the antitryptic activity of the blood. The difference is not so evident when larger amounts of serum are used, as here there is an

15. Folin, O., and Denis, W.: Jour. Biol. Chem., 1911-12, xi, 527.
16. Jobling, J., and Petersen, W.: Jour. Exper. Med., 1914, xix, 239.

excess of the enzyme-inhibiting agent over that necessary to neutralize the amount of trypsin used; but in great dilutions the difference is very obvious.

It is of interest to note that in the two cases of iodism the antiferment was much higher than it had been during the course of treatment. This increase in the antitrypsin may be due to the failure of the iodin to combine with the unsaturated fatty acids, or to an increase of lipoids following the destruction and disintegration of cells as a result of the toxic action of the iodin. It is probably due to the latter factor. It is possible that when large doses of iodids are given there may be localized areas in which the antiferments are completely neutralized; with a consequent destruction of cells by the ferments present and a liberation of lipoids. Thus an increase in antitrypsin is found in almost every case in which a protein intoxication causing cellular injury with mobilization of lipoids is induced experimentally, as after anaphylactic shock, after burns, after serotoxin and anaphylatoxin injection. The iodin may also combine with and neutralize the protective substances in the cell wall and thus permit the ferments to act on them. This may partially explain the toxic action of iodin.

We have recently shown[17] that serum deprived of its antitrypsin becomes toxic for the species from which it is obtained. If guinea-pig serum is shaken thoroughly with two volumes of chloroform and then placed in the incubator for one hour, it becomes so toxic that 2 or 3 c.c. injected intravenously will kill a guinea-pig weighing from 250 to 300 gm. If the mixture of serum and chloroform is permitted to remain in the incubator twenty-four hours, 0.3 c.c. will frequently kill a guinea-pig of this weight. The toxicity of serum treated in this manner is due to the fact that the chloroform removes the antitrypsin, and when this occurs, the ferments, which are normally present, act on the unprotected serum proteins and produce the toxins. Autolysis occurs to a very slight degree during the first hour in the incubator, but after twenty-four hours there is a considerable increase in noncoagulable nitrogen. Up to a certain point the toxicity increases in proportion to the degree of autolysis, but it then decreases rapidly, owing to further cleavage of the toxic substances. Similar results may be obtained with any agent which absorbs the antitrypsin. Thus we have found that kaolin, agar, certain toxins and bacteria act in the same manner, though to a less degree. The antitryptic action of the serum may be destroyed without removing the lipoids. Certain oxidizing agents, such as iodin, saturate the unsaturated carbon bonds of the fatty acids, and in this way destroy their antitryptic action, and render the serums toxic. In our study of these toxins we found that the

17. Jobling, J., and Petersen, W.: Jour. Exper. Med., 1914, xix, 480.

toxicity of the serums treated by the different methods depended on the degree to which the antitrypsin had been removed. Autolysis of the serum also depends on this factor.

If the action of the iodin in causing absorption of necrotic material is due to the general lowering of the antitrypsin, large doses should cause an increase in the nitrogen output owing to the increase of proteolysis. The results of a number of experiments with dogs indicate that the iodids do increase the nitrogen output, but these experiments are not sufficiently advanced to enable us to report on them at this time.

TUBERCULOSIS

There is a general impression among clinicians that iodids are harmful in tuberculosis, as they promote the spread of the infection by causing a softening of the tubercles, and also interfere with connective-tissue formation. On the other hand, L. Bondreau[18] regards iodin as a specific in tuberculosis. He begins treatment with small amounts of the tincture (the French tincture contains 8.5 per cent. of iodin in 95 per cent. alcohol), and increases the dose to 100 drops a day. He states that some of the patients pushed the doses themselves to 200 or 300 drops a day, and one patient took 400 drops a day without the slightest inconvenience.

Loeb and Michaud[19] found that when iodin compounds were injected into the body tuberculous areas took up more iodin than the other tissues. They observed that a tuberculous rabbit's eye contained about twice the amount of iodin present in the normal one, and that caseous lymph-glands of guinea-pigs contained more iodin than any of the normal organs. Wells and Hedenberg[20] repeated the work of Loeb and Michaud, but in addition made experiments to determine the power of necrotic tissue in general to take up and hold iodin. The authors found that tuberculous lymph-glands do take up relatively more iodin from the blood than from the liver, spleen and other glands of the same animal. When the caseous material was abundant enough to permit of separation from the rest of the gland substance, it was found to contain more iodin than did the non-caseous portion. An important part of their work was the demonstration that iodin was taken up equally well by necrotic tissues and exudates produced experimentally. They conclude that the large amount of iodin present in necrotic tissues, whether tuberculous or otherwise, is dependent on

18. Bondreau, L.: Jour. de méd. de Bordeaux, 1914, lxxxv, 1.
19. Loeb, O., and Michaud: Biochem. Ztschr., 1907, iii, 301.
20. Wells, H., and Hedenberg, O.: Jour. Infect. Dis., 1912, xi, 349.

purely physical conditions, and not on a chemical attraction or physical absorption.[21]

Since the reports of Mosetig and Moorhof,[22] iodin in the form of iodoform has been used extensively in the treatment of local tuberculous conditions. Bruns and Nauwerck[23] found that the walls of abscesses treated in this manner were invaded by leukocytes, but they ascribed the disappearance of tubercle bacilli in the inflated tissues to the germicidal action of the iodoform. Heyn and Rovsig[24] and others, however, showed that iodoform has no germicidal action on tubercle bacilli. In 1904 Heile[25] demonstrated the presence of proteolytic ferments in the pus of tuberculous abscesses treated with iodoform, and ascribed the curative action of the iodoform to the accumulation of leukocytes. Weil[26] injected iodoform-glycerin mixtures subcutaneously into both healthy and tuberculous individuals in order to study their influence on the blood. Immediately following the injection there was an increase in the polynuclear cells and a decrease in the number of lymphocytes, but this was soon followed by an increase in the lymphocytes and a decrease in the polynuclears. Most of the investigators believe that the active component of the iodoform is the iodin, and as it is known that the administration of iodin causes an increase in the number of lymphocytes in the blood, Gianasso[27] and others ascribe its action to these cells. According to Bartel and Neuman,[28] the lymphocytes contain substances which neutralize the toxins of the tubercle bacilli, and Bergell[29] believes that this action of the lymphocytes is due to their containing lipase which acts on the neutral fat of the tubercle bacilli. Rothschild[30] believes that iodin stimulates phagocytosis as he found that a much larger number of the tubercle bacilli in the sputum of tuberculous patients receiving iodids were intracellular.

In our work[31] on the antiferments contained in tubercle bacilli and in tuberculous caseous material, we found that the enzyme inhibiting

21. In a recent paper Lewis and Krauss (Jour. Biol. Chem., 1914, xviii, 313) have demonstrated that tuberculous tissue from animals which were never under iodin treatment may contain very appreciable amounts of iodin, thus throwing some doubt on the conclusions reached by Loeb and Michaud and by Wells and Hedenberg.

22. Mosetig and Moorhof: Wien. med. Wchnschr., 1880, xxx, 1174.

23. Bruns, P., and Nauwerck, C.: Beitr. z. klin. Chir., 1887, iii, 133.

24. Heyn, C., and Rovsig, T.: Fortschr. d. Med., 1887, v, 258.

25. Heile: Ztschr. f. klin. Med., 1904, lv, 508.

26. Weil, W.: Ztschr. f. Chemotherap., 1913, Orig., i, 412.

27. Gianasso: Referred to in München. med. Wchnschr., 1905, lii, 1990.

28. Bartel, J., and Neuman, W.: Centralbl. f. Bakteriol., 1905-1906, Orig., xl, 723.

29. Bergell: München. med. Wchnschr., 1910, lvii, 1683.

30. Rothschild, W.: Deutsch. med. Wchnschr., 1913, xxxix, 404.

31. Jobling, J., and Petersen, W.: Jour. Exper. Med., 1914, xix, 251; ibid., 1914, xix, 383.

action was due to the unsaturated fatty acid radicles of the lipoids. At first we believed that this action was due entirely to the soaps of the unsaturated fatty acids, but subsequent work showed that a large portion of the enzyme-inhibiting agents could be removed by extracting with chloroform. The substances contained in the chloroform extracts are not active as antienzymes when suspended in salt solution, as they are insoluble; but the sodium soaps prepared from these acids are active, and we found that their activity was in proportion to the degree of their unsaturation.

In our study of soaps as enzyme-inhibiting agents[16] we found that certain unsaturated fatty acids in the form of soaps were very active as antiferments, but that this action was lost if the acids were first saturated with iodin. These experiments were repeated with the chloroform extracts of tuberculous caseous material and with unextracted caseous material, with the result that the soaps prepared from the chloroform extracts became inactive, and the caseous matter which, previous to treatment with iodin, had not been acted on by trypsin, became readily attacked. The loss of antienzyme action cannot be attributed to any activating influence on trypsin, as iodin inhibits the action of this ferment.

Thus we have definite evidence of the action of the iodids on tuberculous tissue, and the explanation of the well-known clinical observation that iodids cause tubercle bacilli to appear in the sputum of patients with pulmonary tuberculosis, though they were previously absent. When iodids are taken into the tissues a portion of the iodin is liberated and combines with the unsaturated carbon atoms of the fatty acids. As soon as this occurs in necrotic tissue to a degree sufficient to lower or remove the antiferment action, autolysis ensues, as in most instances ferments are present. That the inorganic iodids diffuse readily throughout caseous matter and are thus in a position to furnish the iodin has been shown by Loeb and Michaud, and Wells and Hedenberg.

Tubercles and caseous areas may be present in the lung, but unless they open into the air passages tubercle bacilli may be absent in the sputum. If iodids are now given, the caseous matter begins to soften, and is more likely to rupture into the bronchi, and the bacilli then discharged in the sputum. A somewhat similar explanation may be advanced to explain the softening and rupture of caseous areas, as in lymph-glands, when they are secondarily invaded by streptococci, staphylococci, etc. With the invasion of the infecting organism there is an increase of the blood-supply and an infiltration with polymorphonuclear cells; the increased blood-supply tends to dilute and wash out the excess antiferment, and the ferments liberated from the pus-

cells, with that already present, overcome the antiferment remaining, and softening occurs.

The sudden discharge of the softened caseous material into the bronchi as a result of the action of the iodin would also explain the occurrence of hemorrhages, as it would leave unsupported any blood-vessels traversing the mass whose walls had been involved in the tuberculous process to a degree that would render them unable to withstand the blood-pressure without some outside support. We must bear in mind the possibility and, in fact, probability, that with the softening and absorption of these caseous areas, the tubercle bacilli may be disseminated. The action of the iodids in causing a general reduction in the antiferments of the serum must also be remembered; this reduction in the serum antitrypsin would aid in bringing about the softening and removal of the caseous material.

SYPHILIS

Clinical experience teaches us that in the tertiary stage of syphilis iodin is almost a specific in bringing about the amelioration of symptoms and the disappearance of lesions, and yet little is known concerning the means by which these results are obtained. In reviewing the literature it was found that literally hundreds of articles had been written on the action of iodin in syphilis, but not one gave a rational explanation.

In order to arrive at some understanding concerning the action of iodin in syphilis two points must be considered: First, Does it destroy the infecting organism? Or, second, does it merely bring about resolution of the process, and leave the infecting organism to produce similar lesions?

Authorities on this subject are unanimous in the belief that iodids are not curative in the sense that they prevent the return of the lesions; this can be accomplished only when the iodids are combined with some other form of treatment. Tomasczawski[32] found that the administration of iodin does not prevent the development of experimental syphilis in monkeys and rabbits; neither has it a curative action; but iodized animals recovered quickly when given mercury. That iodin does penetrate into syphilitic tissues has been shown by O. Loeb.[33] This author made quantitative determinations of the amount of iodin in the blood and lymph-glands of syphilitic patients who had received large doses of sodium iodid. He found that the unsoftened lymph-glands contained 3.3 times and the softened glands 6.2 times the

32. Tomasczawski: Deutsch. med. Wchnschr., 1910, xxxvi, 653.
33. Loeb, O.: Arch. f. exper. Path. u. Pharmakol., 1912, lix, 108.

amount of iodin present in the blood. He states that most of the iodin was present as an organic compound which was insoluble in alcohol.

Wells criticizes the technic used by Loeb, and states that he always obtained larger amounts of iodin in the blood. In reply to the criticism of Wells and Hedenberg, Loeb[34] states that iodin is not present in syphilitic tissues merely as the result of diffusion, but that it exists as a true chemical combination with the constituents of the tissues.

As experimental work and clinical observations have demonstrated that the iodids do not destroy the infecting organism, we must assume that the results obtained are due to the power the iodids possess of causing resolution of the lesions present. That this actually occurs will be attested to by every clinician of experience.

Owing to its scarcity we have not been able to examine material from gummas, and so we are unable to state positively that the anti-enzymes present are similar to those found in tuberculous caseous matter; but it is probable that the same agents are active here as in those anemic infarcts in which autolysis does not occur. If this assumption is correct, it is not difficult to explain why large gummas rapidly disappear when the patient is brought under the influence of iodids. It is due to the fact that the unsaturated fatty acid radicals which inhibit autolysis have become saturated with iodin. As soon as this occurs, the ferments which are present, or which may be brought in, become active, autolysis takes place and the necrotic tissue is absorbed. Here, also, the local action of the ferments is made less difficult by the reduction of the antienzyme in the circulating blood. It must be borne in mind that the iodids are not remarkably effective in the earlier stages of syphilis when necrosis of tissue is not so evident.

If the foregoing interpretation of the action of iodin is correct, it gives the clinician a rational idea of what he is accomplishing when he gives iodids to a patient in the tertiary stage of syphilis. According to this view, iodin neutralizes the action of the agents which prevent solution and absorption of necrotic tissue, and at the same time lays bare to the action of the real germicidal agent the infecting organism which previously had been protected by the necrotic tissue. With the exposure of the infecting organism, such agents as mercury and salvarsan would be much more effective.

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34. Loeb, O.: Therap. Monatsch., 1913, p. 178.

CASE 1.—B. S. Luetic. Positive Wassermann; no lesions.

TABLE 1.—INHIBITION IN CASE 1

Date	KI	Serum				
		0.1 c.c. Per Cent.	0.075 c.c. Per Cent.	0.05 c.c. Per Cent.	0.025 c.c. Per Cent.	0.01 c.c. Per Cent.
4/ 9/14	0	80	79	46	19	5
5/ 6/14	34	88	79	60	0	0
5/14/14	120	75	80	19	0	0

Treatment was commenced with 10 drops of a saturated solution three times a day, and the patient ordered to increase 1 drop with each succeeding dose.

The differences are very slight, if any, when large amounts of serum are used, but with greater dilution the influence of the iodids is obvious.

CASE 2.—S. S. Luetic. Perforating ulcer of palate. Improved under treatment.

TABLE 2.—INHIBITION IN CASE 2

Date	KI	Serum				
		0.1 c.c. Per Cent.	0.075 c.c. Per Cent.	0.05 c.c. Per Cent.	0.025 c.c. Per Cent.	0.01 c.c. Per Cent.
4/ 9/14	0	85	73	48	25	5
5/ 7/14	102	86	86	33	25	0
5/14/14	120	81	44	5	0	0

The treatment ordered was the same as in the preceding case. The patient continued taking for two weeks the same dose with which she had begun; it was then increased gradually and the day the second test was made she was taking 102 drops.

CASE 3.—A. M. Luetic. Tertiary stage. No symptoms.

TABLE 3.—INHIBITION IN CASE 3

Date	KI	Serum				
		0.1 c.c. Per Cent.	0.075 c.c. Per Cent.	0.05 c.c. Per Cent.	0.025 c.c. Per Cent.	0.01 c.c. Per Cent.
3/25/14	0	90	80	63	30	17
4/20/14	88	70	56	25	17	0
5/ 6/14	102	60	30	0	0	0

The patient began with the usual amount, and increased it 1 drop each dose.

CASE 4.—S. Luetic. Tertiary stage. Positive Wassermann; no symptoms.

TABLE 4.—INHIBITION IN CASE 4

Date	KI	Serum				
		0.1 c.c. Per Cent.	0.075 c.c. Per Cent.	0.05 c.c. Per Cent.	0.025 c.c. Per Cent.	0.01 c.c. Per Cent.
3/25/14	0	92	86	38	26	26
4/14/14	80	88	80	38	20	5
4/21/14	101	88	85	75	30	20
4/29/14	120	80	56	30	5	0
5/13/14	180	92	85	50	30	0

The treatment ordered was the same as in the preceding cases. At the time the last specimen of blood was taken the patient showed symptoms of iodism with well-marked rash. It is interesting to note that two cases showed iodism, and in both the antitryptic strength of the serum was as high as, if not higher, than in untreated cases.

CASE 5.—N. M. Non-syphilitic.

TABLE 5.—INHIBITION IN CASE 5

Date	KI	Serum				
		0.1 c.c. Per Cent.	0.075 c.c. Per Cent.	0.05 c.c. Per Cent.	0.025 c.c. Per Cent.	0.01 c.c. Per Cent.
3/25/14	0	89	89	69	17	5
5/20/14	?	83	63	38	0	0
5/26/14	45	75	80	56	25	0

The patient took her medicine irregularly. The amount taken at the time the second test was made is not known; but the results indicate that she was taking more than when the third test was made.

CASE 6.—J. P. Secondary stage. No symptoms.

TABLE 6.—INHIBITION IN CASE 6

Date	KI	Serum				
		0.1 c.c. Per Cent.	0.075 c.c. Per Cent.	0.05 c.c. Per Cent.	0.025 c.c. Per Cent.	0.01 c.c. Per Cent.
3/25/14	0	90	90	90	33	25
4/14/14	40	90	92	70	30	20
4/21/14	84	88	88	Lost	33	30
4/29/14	100	88	80	75	19	19
5/13/14	145	92	88	48	5	0

The usual treatment was given.

CASE 7.—S. F. Luetic. Positive Wassermann. Psoriasis-like lesion.

TABLE 7.—INHIBITION IN CASE 7

Date	KI	Serum				
		0.1 c.c. Per Cent.	0.075 c.c. Per Cent.	0.05 c.c. Per Cent.	0.025 c.c. Per Cent.	0.01 c.c. Per Cent.
4/14/14	0	90	90	80	26	19
4/25/14	96	81	80	56	19	5
5/ 6/14	114	83	69	40	19	5
5/11/14	168	81	88	52	5	0
5/23/14	200	86	70	63	0	0

The treatment ordered was the same as in the preceding cases.

CASE 8.—G. H. Luetic. Tertiary stage. Skin lesions on the hands.

TABLE 8.—INHIBITION IN CASE 8

Date	KI	Serum				
		0.1 c.c. Per Cent.	0.075 c.c. Per Cent.	0.05 c.c. Per Cent.	0.025 c.c. Per Cent.	0.01 c.c. Per Cent.
4/14/14	0	89	88	50	25	20
5/ 6/14	70	81	80	40	5	0
5/25/14	100	88	78	80	60	0

The usual treatment was given. At the time the last test was made the patient presented evidences of iodism, with a well-marked rash. Here again the antitryptic strength of the serum is increased.

CASE 9.—J. McD. Luetic. Secondary stage.

TABLE 9.—INHIBITION IN CASE 9

Date	KI	Serum				
		0.1 c.c. Per Cent.	0.075 c.c. Per Cent.	0.05 c.c. Per Cent.	0.025 c.c. Per Cent.	0.01 c.c. Per Cent.
3/30/14	0	90	90	84	75	25
5/ 6/14	100	85	85	52	25	0

The same treatment was instituted.

CASE 10.—J. C. Luetic. Tertiary stage. Aphasia.

TABLE 10.—INHIBITION IN CASE 10

Date	KI	Serum				
		0.1 c.c. Per Cent.	0.075 c.c. Per Cent.	0.05 c.c. Per Cent.	0.025 c.c. Per Cent.	0.01 c.c. Per Cent.
5/ 1/14	0	94	71	44	26	0
5/28/14	90	75	68	25	0	0

The patient received the same treatment.

CASE 11.—J. D. Non-syphilitic.

TABLE 11.—INHIBITION IN CASE 11

Date	KI	Serum				
		0.1 c.c. Per Cent.	0.075 c.c. Per Cent.	0.05 c.c. Per Cent.	0.025 c.c. Per Cent.	0.01 c.c. Per Cent.
4/ 6/14	0	89	70	56	17	5
5/25/14	?	85	80	76	Lost	0
5/29/14	54	87	80	Lost	25	0

The patient did not return to the clinic until about six weeks after his first visit, and he took no medicine during the greater part of this time. Treatment was started again on his second visit.

CASE 12.—T. A. Luetic. Tertiary stage; no symptoms.

TABLE 12.—INHIBITION IN CASE 12

Date	KI	Serum				
		0.1 c.c. Per Cent.	0.075 c.c. Per Cent.	0.05 c.c. Per Cent.	0.025 c.c. Per Cent.	0.01 c.c. Per Cent.
4/29/14	0	81	78	38	20	0
5/13/14	...	83	81	38	Lost	0
5/23/14	125	85	85	77	20	0

Treatment commenced April 29, 1914, with 10 mm. potassium iodid three times a day, and patient increased the dose at irregular intervals. May 26, 1914, patient was taking 125 mm.

CASE 13.—E. W. Luetic. Secondary stage. Positive Wassermann; no symptoms.

TABLE 13.—INHIBITION IN CASE 13

Date	KI	Serum				
		0.1 c.c. Per Cent.	0.075 c.c. Per Cent.	0.05 c.c. Per Cent.	0.025 c.c. Per Cent.	0.01 c.c. Per Cent.
4/ 6/14	0	90	88	56	28	5
4/27/14	0	87	90	69	40	5
5/16/14	126	75	52	5	0	0

The patient continued taking the same quantity two weeks, and then discontinued it altogether until May 27, when she was started on 15 drops three times a day.

OBSERVATIONS ON RENAL FUNCTION IN ACUTE EXPERIMENTAL UNILATERAL NEPHRITIS *

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BOSTON

The study of renal function during the past few years has occupied considerable attention in both clinical and experimental laboratories. A number of different tests have been advocated by different observers, but so far no attempt has been made, in experimental surgery, to compare a variety of these tests on the same animal at the same time. This paper describes experiments which were made to establish an acute unilateral nephritis in dogs, and records the studies on renal function in this condition to determine which of the tests used most commonly in the surgical clinic are of greatest practical value in the diagnosis of one-sided lesions of varying severity.

An experimental one-sided nephritis has already been produced. In 1883, Ribbert[1] excised the medulla of one kidney in rabbits in his experiments on renal physiology. Boyd[2] and Oppenheimer[3] confirmed this method of producing a unilateral lesion by using the same technic. Oppenheimer's work is of especial interest in regard to functional studies on nephritis. By removing the cortex of one kidney, he found that the secretion of urine on that side stopped. But when the medulla was removed, there was an increased output of urine from the affected kidney which contained more sodium chlorid and had a lower freezing-point than the urine from the normal side. Yet the glycosuria resulting from subcutaneous injections of phloridzin was diminished. This, he considered, afforded evidence in favor of tubular resorption. Schlayer's[4] method for producing unilateral lesions consisted of the injection of epinephrin into various points of the renal parenchyma. As a result, he obtained a contracted kidney. Hirsch and Maschke[5]

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1. Ribbert: Ueber Resorption von Wasser in der Marksubstance der Niere, Virchow's Arch. f. path. Anat., 1883, xciii, 169.

2. Boyd: Some Experiments on the Functions of the Medulla of the Kidney, Jour. Physiol., 1902, xxviii, 76.

3. Oppenheimer: Experimentelle Untersuchungen über die Nierentätigkeit und ihre Beziehung zur funktionellen Diagnostik, Verhandl. d. deutsch. Gesselsch. f. Urol., 1909, ii, 289.

4. Schlayer: Ueber künstliche Erzeugung von Schrumpfniere, München. med. Wchnschr., 1909, lvi, 687.

5. Hirsch and Maschke: Experimentelle Untersuchungen über Nephritis, Berl. klin. Wchnschr., 1912, xlix, 145.

introduced the actual cautery into different parts of one kidney and obtained foci of scar tissue on that side. Brewer[6] caused pyelonephritis by the injection of pathogenic bacteria into the proximal segment of the ligated ureter, and Stewart[7] made a similar picture by the implantation of the ureter into the wall of the intestine. These various experiments, however, were designed to produce a chronic nephritis or depended on infection or on the introduction of artificial factors which would render the animals unfit for further studies.

For our purposes, Ribbert's[8] later method, as used by Baehr,[9] promised more satisfactory results. Ribbert exposed the renal artery of one kidney in rabbits and injected directly into it a solution of iodin which was perfused through the whole kidney by the arterial blood. Baehr, following this technic, injected the renal artery in the same way with iodin, croton oil, potassium chromate and uranium nitrate. The last substance produced marked unilateral glomerular lesions in rabbits, with little tubular destruction. By different degrees of dosage and by varying the length of time which the disease was allowed to run, various stages of acute, subacute or chronic one-sided nephritis were obtained. In our experiments, Baehr's method with uranium nitrate was followed with a few changes.

The introduction of ureteral catheterization into renal surgery opened up a brilliant field for the study of the urine excreted simultaneously from each kidney. By this method, the urine from one kidney could be compared with the urine from the other, and a number of different observations could be made to determine which kidney showed an abnormal function, and to what extent it was damaged compared with the other kidney. It is known that there is a certain variation in the amount of urine and solids excreted from the two kidneys over short intervals of time. But Albarran[10] and Kapsammer[11] have found that these differences diminish with the length of time of observation, and that normally, in an hour, nearly the same amount of urine and solids comes from each side.

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6. Brewer: The Present State of Our Knowledge of Acute Renal Infections; With a Report of Some Animal Experiments, Jour. Am. Med. Assn., 1911, lvii, 179.

7. Stewart: A Study of Ascending Infection of the Kidney Carried Out by the Method of Transplanting the Ureters into the Intestines, Univ. Penn. Med. Bull., 1911, xxiii, 233.

8. Ribbert: Untersuchungen über die normale and pathologische Physiologie und Anatomie der Niere, Bibliotheca Medica, 1896, Part C, No. 4, p. 1.

9. Baehr: Ueber experimentelle Glomerulonephritis (Ein Beitrag zur Lehre der Schrumpfniere), Beitr. z. path. Anat. u. z. allg. Path., 1913, lv, 545.

10. Albarran: Recherches sur le fonctionment normal comparé des deux reins, Ann. d. mal. d. org. genito-urin., 1904, xxii, 81.

11. Kapsammer: Uber Ureterenkatheterismus und funktionelle Nierendiagnostik, Wien. klin. Wchnschr., 1903, xvi, 1417.

Certain physical, chemical and excretory properties of the urine from the two kidneys have been compared to estimate differences in renal function of the two organs under pathological conditions. Von Korányi[12] introduced the determination of the freezing-point of urine as an index for the functional capacity of the two kidneys. In general, he found that the concentration of the urine was less as the severity of the disease increased. Many subsequent observers have applied this method as a test for function in unilateral disease. The results obtained from it have disagreed. The bulk of evidence shows that the freezing-point of urine determines which kidney is functioning to best advantage, but that this test is by no means quantitatively accurate.

Turner[13] made observations on the electrical conductivity of urine under various conditions. He discovered that its electrical resistance in ohms was inversely proportional to its sodium chlorid concentration, and believed that this test, on account of its relative simplicity and the small amount of urine required in performing it, would be valuable in surgery as a means of studying the function of the individual kidney. Loewenhardt[14] confirmed these results by showing that under normal conditions the electrical resistance of the urine from each kidney was nearly the same, but when the function of the two kidneys varied, marked differences in electrical conductivity of the separated urines were found. A powerful advantage for this test, he declared, lay in the fact that since small amounts of urine were needed, the length of time for ureteral catheterization could be materially shortened. These findings, however, have not been accepted by many observers. Gottstein[15] objects to the test after careful review of the literature and from his own experience. Since electrical conductivity does not deal with the number of molecules in solution, but merely with the number of ions, it offers no information as to the total concentrative powers of the kidney, and tells but little more in regard to the degree of renal injury than a specific gravity determination.

The excretion of sodium chlorid, nitrogen or urea from the two sides has been compared in suspected unilateral disease. The amount of nitrogen or urea put out has given the most accurate information in regard to the degree of disease. While Albarran found in normal indi-

12. Von Korányi: Physiologische und klinische Untersuchungen über der osmotischen Druck thierischen Flüssigkeiten, Ztschr. f. klin. Med., 1897, xxxiii, 1; ibid., 1898, xxxiv, 1.

13. Turner: The Electrical Conductivity of the Blood and Urine in Health and in Disease, and as a Test of the Functional Efficiency of the Kidney, Edinburgh Med. Jour., 1907, N. S., xxi, 318.

14. Loewenhardt: Weitere Ergebnisse der Bestimmung der elektrischen Leitfähigkeit des Harnes, Deutsch. Gesellsch. f. Urol., 1909, ii, 281.

15. Gottstein: Der heutige Stand der funktionellen Nierendiagnostik, Ergebn. d. Chir. u. Orthopädie, 1911, ii, 417.

viduals that the actual amount of urea from the two kidneys was nearly the same over a given interval, Barringer[16] showed that in disease its total excretion varied, diminishing in almost direct proportion to the degree of injury found in one or the other organ. Many other writers have confirmed this observation.

Of the substances found in the urine under normal conditions, Wohlgemuth[17] has advocated the estimation of diastase as a test for the function of the two kidneys. He believes that this determination affords a simple means for estimating differences in function of the two kidneys when one is diseased, and that the amount of ferment excreted varies directly with the degree of injury on the affected side. His results in bilateral nephritis have been substantiated by von Benczur,[18] Geyelin,[19] Hirata,[20] Marino,[21] Rosenthal[22] and Wynhausen.[23] Few confirmatory studies have been made with the test in surgery except by Geraghty, Rowntree and Carey.[24] At present the true value of this method is undetermined.

Finally, Palmer and Henderson[25] have found that the urinary acidity as estimated by its hydrogen ion concentration shows marked variation in different types of nephritis. It seemed possible that this test in unilateral disease might give interesting results.

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16. Barringer: The Comparison of the Total Urea Excreted by Each Kidney in Surgical Diseases of These Organs; Its Value in Estimating the Functional Capacity and Pathological Changes of Kidneys, Surg., Gynec. and Obst., 1908, vii, 651.

17. Wohlgemuth: Ueber eine neue Methode zur quantitativen Bestimmung des diastatischen Ferments, Biochem. Ztschr., 1908, ix, 1; Beitrag zum Verhalten der Diastase im Urin, ibid., 1909, xxi, 432; Experimentelle Beiträge zur Prüfung der Nierenfunktion, Ztschr. f. Urol., 1911, v, 801.

18. Von Benczur: Beitrag zur klinischen Verwertbarkeit der Diastasemenge in Blutserum und Urin, Wien. klin. Wchnschr., 1910, xxiii, 890.

19. Geyelin: A Clinical Study of Amylase in the Urine, with Special Reference to the Phenolsulphonephthalein Test, THE ARCHIVES INT. MED., 1914, xiii, 96.

20. Hirata: Beitrag zum Verhalten der Diastase im Blut und im Urin beim Kaninchen, Biochem. Ztschr., 1910, xxviii, 23.

21. Marino: Ueber die diagnostische Bedeutung der Diastaseausscheidung im Harn, Deutsch. Arch. f. klin. Med., 1911, ciii, 325.

22. Rosenthal: Zur Frage der Ausscheidung von disastatischem Ferment im Urin, Deutsch. med. Wchnschr., 1911, xxxvii, 923.

23. Wynhausen: Quantitative Diastasebestimmungen im Harn, besonders ihre Beziehung zur Nephritis und zum Diabetes mellitus, Berl. klin. Wchnschr., 1910, xlvii, 2107.

24. Geraghty, Rowntree and Carey: The Value and Limitation of Diastase, Urea and Phthalein in Estimating Renal Function in Association with Ureteral Catheterization, Ann. Surg., 1913, lviii, 800.

25. Henderson and Palmer: On the Intensity of Urinary Acidity in Normal and Pathological Conditions, Jour. Biol. Chem., 1913, xiii, 393; Clinical Studies on Acid Base Equilibrium and the Nature of Acidosis, THE ARCHIVES INT. MED., 1913, xii, 153.

Various substances have been injected into the body and their excretion in the urine followed as tests to illustrate the comparative functions of the two kidneys. Such tests in general have depended on the kidney's ability to rid itself of dyes or drugs or to produce a glycosuria from phloridzin.

Many dyes have been tried as tests for renal function, but at present two are generally accepted as being most valuable. Voelcker and Joseph[26] injected a solution of indigocarmin intramuscularly, noted its time of appearance in the urine, and determined by colorimetry the total amount excreted in a given interval. In general, both the time of appearance and the amount excreted varied with the severity of the existent nephritis. Their results have been confirmed by Baetzner,[27] Ehrich,[28] Roth,[29] and Tanaka,[30] who emphasized that the time of appearance, though usually important, might be misleading in certain cases; and that, therefore, the actual amount excreted was of greater significance. Gottstein considers indigocarmin the most satisfactory single test for renal function which is used.

Rowntree and Geraghty[31] made use of phenolsulphonephthalein as a test for renal function, showing it to be an excellent index of both unilateral and bilateral kidney disease. Their original work has been supported by many observers, among others Behrenroth and Frank,[32] Cabot and Young,[33] Deutsch[34] and Keyes and Stevens.[35]

Von Mering[36] discovered that a characteristic of phloridzin, following its subcutaneous injection, was the production of a glycosuria in

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26. Voelcker and Joseph: Funktionelle Nierendiaguostik ohne Ureterenkatheter, München. med. Wchnschr., 1903, l, 2081.

27. Baetzner: Funktionelle Nierendiagnostik, Berl. klin. Wchnschr., 1912, lxix, 1521.

28. Ehrich: Diagnostischer Wert der Indigokarminprobe bei chirurgischen Nierenerkrankungen, Deutsch. med. Wchnschr., 1911, xxxvii, 526.

29. Roth: Ueber die Unzulänglicheit der Chromocystaskopie für die funktionelle Nierendiagnostik, Ztschr. f. Urol., 1911, v, 439.

30. Tanaka: Bestimmung zur Indigocarminreaktion für die funktionelle Nierendiagnostik, Ztschr. f. Urol., 1911, v, 82.

31. Rowntree and Geraghty: An Experimental and Clinical Study of the Functional Activity of the Kidneys by Means of Phenolsulphonephthalein, Jour. Pharmacol. and Exper. Therap., 1910, i, 579.

32. Behrenroth and Frank: Klinische und experimentelle Untersuchungen über die Funktion der Niere mit Hülfe der Phenolsulphonephthalein Probe, Ztschr. f. exper. Path. and Therap., 1913, xiii, 72.

33. Cabot and Young: Phenolsulphonephthalein as a Test of Renal Function, Tr. Am. Assn. G.-U. Surg., 1911, vi, 136.

34. Deutsch: Funktionelle Nierenprüfung mittels Phenolsulphonephthalein, Wien. klin. Wchnschr., 1912, xxv, 1217.

35. Keyes and Stevens: A Clinical Study of Renal Function by Means of Phenolsulphonephthalein, Am. Jour. Urol., 1911, vii, 367.

36. Von Mering: Ueber kunstlichen Diabetes, Centralbl. f. d. med. Wissensch., 1885, xxiii, 531.

actively functioning kidneys. Casper and Richter[37] made use of this fact as the basis for a test of renal function. They injected phloridzin subcutaneously, noted the appearance time of sugar in the urine coming from each kidney, and compared the total amount of sugar excreted over a given period of time. They believed that, if one kidney were diseased, it put out less sugar than the normal kidney, the discrepancy varying in proportion to the severity of the lesion. Thus the test was not only qualitative, but also quantitative. Other observers, however, have not confirmed Casper and Richter. Though this test has many adherents, it is believed that the phloridzin test alone is not of great value.

From this short review, it is seen that tests for renal function fall into two distinct groups. The first group depends on variations in the physical and chemical properties of the urine coming from each kidney. The most important of such tests are the determination of the freezing point of the urine and the comparative amounts of nitrogen, urea and diastase excreted in a known period of time. The second group of tests depends on the ability of the kidney to excrete from the blood abnormal substances which are introduced into the circulation. The most important of this group are the indigocarmin and phenolsulphonephthalein tests. The phloridzin glycosuria test, though strictly speaking not belonging in this group, may be included for convenience.

A number of clinical observations have been made to compare certain of these tests to decide which single one is of the greatest value. Casper and Richter compared the phloridzin test with freezing-point determinations in a number of cases. The results of these tests agreed closely. When one kidney was diseased the molecular concentration of that urine was low, the glycosuria was delayed in appearance and small in amount. When no lesion existed, the concentration of the two urines was nearly the same and the time of appearance of sugar and the amount excreted from both sides were alike. Roth[38] made use of indigocarmin, phloridzin and freezing point determinations in a series of comparative studies. The excretion of indigocarmin and the amount of phloridzin glycosuria paralleled each other and bore a close relationship to the freezing point. All tests pointed out the diseased kidney. Yet Roth,[39] in a later paper, expressed the opinion that the indigocarmin test was less delicate than the other two. Unterberg[39] compared the excretion of sodium chlorid and urea with freezing-point

37. Casper and Richter: Functional Diagnosis of Kidney Disease, 1903, P. Blakiston's Sons & Company, Philadelphia.

38. Roth: Zur Bewertung der Indigkarminmethode für funktionelle Nierendiagnostik, Verhandl. d. deutsch. Gesellsch. f. Urol., 1909, ii, 305.

39. Unterberg: Der praktische Wert der funktionellen Nierenuntersuchungen bei chirurgischen Erkrankungen der Nieren, Ztschr. f. Urol., 1909, iii, 687.

determinations and with the phloridzin test. There was a parallelism between all the tests. The freezing point varied with the amount of urine obtained, but in cases of unilateral disease it was always nearer to zero on the diseased side than on the normal side. In such cases, the chlorid and urea excretions were usually diminished.

Baetzner compared the excretion of indigocarmin with the freezing point and found that as the excretion of the dye diminished, the molecular concentration of the urine was less, and that both these tests ran parallel with the degree of renal injury. Goodman and Kristeller,[40] and Thomas[41] compared the excretion of phenolsulphonephthalein with that of indigocarmin in one-sided kidney disease. The two dyes were eliminated in amounts closely parallel; the total amount of indigocarmin excreted in proportion to the amount injected was approximately one-half that of phenolsulphonephthalein excreted. Keyes and Stevens compared the excretion of phenolsulphonephthalein with that of urea from separately catheterized kidneys. The cases which justified comparison gave the same results and showed the same ratio of functional ability. Stevens[42] compared the phenolsulphonephthalein test with phloridzin glycosuria and with the excretion of urea. In both normal and pathological cases, these tests gave similar results. Finally, Geraghty, Rowntree and Carey compared the excretion of phenolsulphonephthalein with urea and diastase in a series of cases. They felt that the phenolsulphonephthalein test was the most significant, that diastase was of value in the majority of cases as indicating which kidney was the more diseased, and that urea estimations almost invariably corroborated the phenolsulphonephthalein findings. A patent disadvantage of the diastase test lay in the fact that dilution of the urine affected it to a more marked extent than it did the other tests — a point which Wohlgemuth has emphasized in his experiments on dogs.

Thus, on the whole, a striking parallelism appears to exist between the tests for renal function which are generally used in surgical diseases of the kidney. Although the amount of urine excreted from the two sides may vary, its molecular concentration diminishes in proportion to the severity of the disease; it contains less nitrogen, urea and diastase; the diseased kidney in proportion to its lesion is less capable of excreting indigocarmin, phenolsulphonephthalein and sugar after

40. Goodman and Kristeller: The Value of Phenolsulphonephthalein in Estimating the Functional Efficiency of the Kidneys, Surg., Gynec. and Obst., 1911, xii, 56.

41. Thomas: The Quantitative Determination of Functional Renal Sufficiency by the Duboscq Colorimeter: Indigo-Carmine versus Phenolsulphonephthalein, Am. Jour. Med. Sc., 1911, cxlii, 376.

42. Stevens: The Comparative Value of Modern Functional Kidney Tests, Jour. Am. Med. Assn., 1914, lxii, 1544.

the injection of phloridzin. In other words, all these various tests point to the same findings. The tests for renal function used in surgery are based on the facts that a diseased kidney is incapable of excreting solids, and that the degree of impairment of this fundamental function parallels in a general way the degree of existent disease. Therefore, the important feature in the selection of a test for renal function, when the urine from the two kidneys is compared, is to choose that one which is simplest for both surgeon and patient to perform, but which is delicate enough to point out the degree of existent disease. Tests for renal function on our dogs with unilateral nephritis were undertaken to determine this point experimentally.

METHOD

Dogs were anesthetized with morphin and ether. In a few animals, abdominal section through the left rectus incision was made under aseptic precautions. The left kidney was freed from its capsule and its artery and vein were dissected clean by scissors and by wiping with dry gauze. Every effort was made to avoid rupture of nerve fibers. Rubber-tipped serrefines were placed separately on both vein and artery. The kidney itself was then delivered through the abdominal wound in such fashion as to expose the renal artery to best advantage without undue tension. One c.c. of distilled water which contained the desired dose of uranium nitrate was then injected into the vessel from a 2 c.c. Record syringe with a fine pointed needle, the tip of which was bent at right angles. In a few cases in which the renal artery was doubled, each branch was clamped and was injected with half the dose. In other animals, only one branch of the renal artery was injected. In a few experiments, 2 or 5 c.c. of injection fluid were used.

After the artery was injected the arterial clamp was removed for a few seconds in order to distribute the uranium through the kidney substance as diffusely as possible. The slight bleeding at the point of puncture occasioned by this procedure was readily controlled, and the kidney as a whole became engorged. The arterial clamp was replaced. After intervals of from thirty seconds to five minutes, the point of the needle was inserted into the renal vein, and 5 c.c. of blood from the kidney were aspirated into the syringe. Whatever bleeding occurred around the needle point was controlled by walling-off sponges to prevent systemic absorption of the poison. Finally both the arterial and venous clamps were removed, the kidney replaced in its normal position and the wound closed according to usual methods.

Virtually, the same technic was used in all our experiments. The only modification in our later studies was to use a lumbar incision for exposing the kidney, instead of reaching it through the peritoneum.

In this way, a smaller incision could be made, the muscles could be separated by blunt dissection without bleeding, and the kidney could be exposed and delivered into the wound through the back with slight handling. Great care was used throughout not to traumatize the kidney.

As our primary object was to produce different degrees of pathological change, the dosage of the drug varied in individual cases. The largest amount given was 1 mg. of uranium per kilogram of body weight, the smallest dose was $\frac{1}{20}$ mg. per kilogram of body weight. Slightly less than 0.1 mg. per kilogram of body weight was found to produce a well-marked nephritis in twenty-four hours; this consequently was the dosage which was used in the majority of our experiments.

A few typical protocols with photomicrographs of the two kidneys are given to demonstrate the efficacy of the technic.

EXPERIMENT 1.—*Severe Nephritis.*—Dog 1, weight 7 kg.

March 16: Ether-morphin anesthesia. Left rectus incision. The left kidney was exposed and delivered through the wound after the renal vessels were dissected free and clamped. One mg. per kilogram body weight of uranium nitrate in 2 c.c. of distilled water was injected into the renal artery. The arterial clamp was removed and reapplied at once. After one minute the renal vein was punctured and the blood was removed by pressure and suction. The clamps were then removed from the vessels, the kidney was replaced in normal position and the wound sewn up.

March 17: Animal appeared in good condition. It was killed twenty-four hours after operation. The right kidney weighed 40 gm. and appeared normal. The left kidney weighed 65 gm. and was dark colored, except in minute areas scattered through the parenchyma which appeared necrotic. Specimens of tissue were obtained from both kidneys, fixed in Zenker's fluid and stained with eosin and methylene blue. Microscopic sections from the right kidney were normal. Sections from the left kidney showed areas of hemorrhagic necrosis in which the normal renal structure was lacking. In other parts many of the glomeruli showed necrosis of the capillary endothelium with fibrinous thrombi in the vessel walls. The tubular epithelium was lacking in certain parts. In others, it had desquamated into the lumen of the tubule, filling it with homogeneous necrotic material and serum. Numerous polymorphonuclear leukocytes were seen throughout the entire kidney structure. On the whole, the histological picture was that of an acute unilateral nephritis with necrosis of the kidney.

EXPERIMENT 2.—*Well-Marked Nephritis.*—Dog 4, weight 9 kg.

March 23: Morphin-ether anesthesia. Left rectus incision. The left kidney was exposed and delivered through the wound after the renal vessels were dissected free and clamped. The renal artery was bifurcate, so that clamps were applied to each branch. Each artery was injected with 0.4 mg. (0.9 mg. per kilogram body weight) of uranium nitrate in 0.5 c.c. of distilled water. The arterial clamps were removed and reapplied at once. After three minutes the renal vein was punctured and the blood was removed by pressure and suction. The clamps were then removed from the vessels, the kidney was replaced in normal position, and the wound was sewn up.

March 24: The animal appeared in good condition. It was killed twenty-four hours after operation. The right kidney weighed 32 gm. and appeared

Fig. 1 (Dog 1).—Right kidney. Eosin-methylene blue staining, × 20. No lesion made out.

Fig. 2 (Dog 1).—Left kidney. Eosin-methylene blue staining, × 20. Necrosis of glomeruli and tubules. Edema. Leukocytic infiltration.

normal. The left kidney weighed 43 gm., and was firm and of dark color. Specimens of tissue were obtained from both kidneys, fixed in Zenker's fluid and stained with hematoxylin and eosin. Microscopic sections from the right kidney were normal. Microscopic sections from the left kidney showed considerable hemorrhage. There were a few small areas of necrosis and of polymorphonuclear leukocytic infiltration. The larger part of the kidney was much less severely damaged. The glomeruli were normal. There was considerable desquamation of epithelium and effusion of serum into the lumen of the tubules, as in the previous experiment, with the formation of similar homogeneous masses, many of which contained leukocytes. There was evidence of tubular regeneration shown by large atypical epithelial cells lining some of the tubules. No mitotic figures were seen. The histological picture, therefore, was that of a moderately severe unilateral nephritis with a small amount of necrosis, but with well-marked tubular destruction.

EXPERIMENT 3.—*Mild Nephritis.*—Dog 9, weight 6.2 kg.

April 10: Ether-morphin anesthesia. Left lumbar incision. The left kidney was exposed and delivered through the wound after the renal vessels were dissected free and clamped. The renal artery was bifurcate so that clamps were applied to each branch. Each artery was injected with 0.3 mg. (0.1 mg. per kilogram body weight) of uranium nitrate in 2.5 c.c. of distilled water. The arterial clamps were removed and were reapplied at once. After two minutes the renal vein was punctured, and the blood was removed by pressure and suction. The clamps were then removed from the vessels, the kidney was replaced in normal position, and the wound was sewn up.

April 13: Following the operation, the animal was in good condition. It was killed seventy-two hours later. The right kidney weighed 14 gm. and the left 12 gm. In the gross, both kidneys appeared normal. Specimens of tissue were obtained from both kidneys, fixed with Zenker's fluid, and stained with hematoxylin and eosin. Microscopic sections from the right kidney were normal. Sections from the left kidney showed less acute changes than the two preceding. There was no evidence of exudation or hemorrhage. The glomeruli were normal. Many of the tubules were filled with homogeneous material like that previously described, and which appeared to come from desquamated epithelium. There was considerable formation of new epithelium, and mitotic figures could be found without difficulty.

These three typical protocols illustrate that it is possible to produce an experimental unilateral nephritis by the method described, causing different degrees of severity according to the amount of poison injected and according to the length of time the disease is allowed to exist. In all our experiments, except those in which insufficient dosage of uranium was given, similar lesions were obtained. In the entire series no pathological change was found in the normal kidney, and in only one observation was thrombosis of the injected renal artery found at necropsy. Thus the method appeared satisfactory for our purposes.

At varying intervals of from twenty-four hours to eighteen days after the initial operation, the dogs were anesthetized with paraldehyd in dosage of 1.7 c.c. per kilogram of body weight. The ureters were freed by lumbar incision and were catheterized separately with fine glass cannulas. The urine from the kidneys was collected in test-tubes. The rate of respiration, the carotid blood-pressure and the rate of urinary outflow were recorded on a kymographion according to usual technic.

The amount of urine required for the various functional tests which were to be studied was so large that it was necessary to stimulate the kidneys by a diuretic. The animals at the beginning of the experiment were given 200 c.c. of water by stomach-tube and 10 per cent. saline solution intravenously. The initial dose used was 20 c.c.; this was repeated often enough to maintain a constant flow of urine. It was realized that this maneuver introduced an abnormal factor into the experiment. It was constant, however, since the sodium chlorid which came to the kidneys at any time was the same on each side. Therefore, the response of the two kidneys was considered as significant as though no diuretics had been used.

After the animal was once anesthetized and catheterized, a uniform rate of urinary outflow soon became established. The subsequent observations were divided into four periods of an hour each. During the first hour, the urine from the two sides was collected and measured. Its specific gravity was obtained by weight; its total sodium chlorid and nitrogen content as well as their concentration per hundred c.c. of urine were found by Volhard's method and Kjeldahl's method; the freezing-point was determined by Beckmann's method; the diastase content by Wohlgemuth's[43] method; the hydrogen ion concentration by Palmer and Henderson's method.

In the second hour the phenolsulphonephthalein test was performed. Rowntree and Geraghty's original technic was used. A solution, 1 c.c. of which contained 6 mg. of the dye, was injected intramuscularly or intravenously. A small amount of alkali was added to the test-tubes which collected the urine from each kidney. The time of appearance of the dye from the two sides was observed and the total amount excreted in an hour from each kidney was estimated in Rowntree and Geraghty's modification of the Autenrieth-Königsberger colorimeter.

Prussian blue, introduced by Schroeder van der Kolk[44] in histology, is recognized as being one of the standard means[45] for staining the renal tubules. It seemed possible that the excretion of this dye might be used as a test for renal function in the same fashion that other dyes are used. A solution was made which contained 100 mg. of potassium ferrocyanid in 1 c.c. of water and was injected intravenously. A small amount of ferric chlorid and dilute hydrochloric acid were added to the test-tubes receiving the urine from the ureteral catheters. As soon as the ferrocyanid appeared in the urine, it was precipitated as a deep

43. Wohlgemuth and Noguchi: Experimentelle Beiträge zur Diagnostik der subcutanen Pankreasverletzungen, Berl. klin. Wchnschr., 1912, xlix, 1069.

44. Schroeder van der Kolk: Quoted by Hartung: Das Mikroskop, 1866, Vieweg und Sohn, Braunschweig, ii, 124.

45. Enzyklopädie der Mikroskopischen Technik, 1910, Urban and Schwarzenberg, Vienna, ii, 321.

blue sediment. The time of appearance of this dye from each kidney was recorded, and the total amount excreted in one hour was quantitated in the Duboscq colorimeter by turbidometry against a standard solution of the dye precipitated in the same fashion and diluted to an appropriate bulk.

The following experiment illustrates the relative accuracy with which such readings could be obtained. A standard solution was made containing 100 mg. of Prussian blue in a liter of water. Other solutions were made containing respectively 90, 80, 70, 60, 50, 40, 30, 20 and 10 mg. of the dye, and were diluted to 1 liter. The solutions were read independently by each of us against the standard. The readings in percentage, and the average reading of our two observations is given in Table 1.

TABLE 1.—READING OF VARIOUS SOLUTIONS AGAINST A STANDARD SOLUTION

	Reading 1 Per Cent.	Reading 2 Per Cent.	Average Reading Per Cent.	Error Per Cent.
100 mg. = 100 per cent. solution	95	90	92.5	2.5
90 mg. = 90 per cent. solution	80	77	78.5	1.5
80 mg. = 80 per cent. solution	69	70	69.5	0.5
70 mg. = 70 per cent. solution	57	60	58.5	1.5
60 mg. = 60 per cent. solution	52	52	52.0	2.0
50 mg. = 50 per cent. solution	42	44	43.0	3.0
40 mg. = 40 per cent. solution	30	34	32.0	2.0
30 mg. = 30 per cent. solution	24	25	24.5	4.5
20 mg. = 20 per cent. solution	*	*	*	*
10 mg. = 10 per cent. solution				

* Too dilute to read = "traces."

Unfortunately, in urine such satisfactory readings were not obtained. In certain cases, on the addition of hydrochloric acid and ferric chlorid, a green precipitate occurred. In others, while the diluted urine appeared blue, in the colorimeter it was of a different shade than the standard, thus interfering with the reading. Hence, in several observations no quantitative readings were attempted. Instead, one urine was compared against the other to show the comparative outputs of the two sides.

During the fourth period the indigo-carmin test was made according to Voelcker and Joseph's technic. Twenty c.c. of a 0.4 per cent. solution of the dye in distilled water were injected intramuscularly or intravenously. The time of appearance of blue in the urine was noted, and the total quantity excreted in an hour was estimated colorimetrically in the Duboscq colorimeter.

Finally, a necropsy of the animal was held, and sections from each kidney were hardened in Zenker's fluid for microscopic study. To illustrate the effect of diuresis on the excretion of diastase, the determination was made in several of the experiments both before and

after the introduction of the sodium chlorid. Indigocarmin and phenolsulphonephthalein were always given in the same animal, either intramuscularly or intravenously, in order to compare their respective rates of excretion by these two forms of injection. The colorimetric estimation of indigocarmin following its intramuscular injection was usually difficult owing to its change in color. This was often obviated by intravenous administration.

The results of these experiments fall into three groups. Group 1 consists of three control animals. Group 2 consists of animals with well-marked nephritis. Group 3 consists of animals showing functional disturbances of the kidney without definite histological changes from the normal. Protocols of these various observations are given.

GROUP 1: CONTROL ANIMALS

EXPERIMENT 4.—Dog 11, weight 16.7 kg. Anesthetized with paraldehyd. Ureteral catheterization after double lumbar incision. Diuresis induced by 150 c.c. of water by stomach-tube, and by intravenous injections of 10 per cent. saline solution. At necropsy, the two kidneys were of equal weight and appeared normal. No abnormal histological changes were found.

TABLE 2.—FINDINGS IN EXPERIMENT 4

	Right Kidney	Left Kidney
Amount of urine, first hour	18 c.c.	14 c.c. ‡
Specific gravity	1.015	1.013
Sodium chlorid per 100 c.c.	.48 gm.	.48 gm.
Total chlorid	86 mg.	67 mg.
Nitrogen per 100 c.c.	.40 gm.	.35 gm.
Total nitrogen	72 mg.	49 mg.
Diastase*	16	16
Hydrogen ionization	8	8.7
Phenolsulphonephthalein period:†		
Amount of urine, second hour	23 c.c.	20 c.c.
Appearance time of dye	5 minutes	5 minutes
Total excretion of dye	22 per cent.	24 per cent.
Indigocarmin period:		
Amount of urine, third hour	20 c.c.	17 c.c.
Appearance time of dye	5 minutes	5 minutes
Total excretion of dye	6 per cent.	6 per cent.
Prussian blue period:		
Appearance time of dye	1½ minutes	1½ minutes

* The diastase reading in this table and others represent the amount of 0.1 per cent. starch solution digested in thirty minutes by 1 c.c. of urine at 37 C. (98.6 F.).

† Phenolsulphonephthalein and indigocarmin given intramuscularly. The indigocarmin excretion was followed for thirty minutes. One specimen of Prussian blue lost.

‡ Slight loss.

EXPERIMENT 5.—Dog 20, weight 13.3 kg. Anesthetized with paraldehyd. Double lumbar incision followed by ureteral catheterization. Diuresis induced by 200 c.c. of water by stomach-tube and by intravenous injection of 10 per cent. saline solution. At necropsy the two kidneys were of equal weight and appeared normal. No abnormal histological changes were found.

TABLE 3.—FINDINGS IN EXPERIMENT 5

	Right Kidney	Left Kidney
Amount of urine, first hour	18 c.c.	19 c.c.
Sodium chlorid per 100 c.c.	1.3 gm.	1.4 gm.
Total chlorid	234 mg.	266 mg.
Nitrogen per 100 c.c.	.54 mg.	.64 mg.
Total nitrogen	97 mg.	121 mg.
Diastase before diuresis	64.5	64.5
Diastase after diuresis	32	32
Freezing-point	—.55°	—.90°
Hydrogen ionization	5.5	5.7
Phenolsulphonephthalein period:*		
Amount of urine, second hour	70 c.c.	60 c.c.
Appearance time of dye	1 45/60 minutes	1 45/60 minutes
Total excretion of dye	40 per cent.	43 per cent.
Indigocarmin period:		
Amount of urine, third hour	55 c.c.	50 c.c.
Appearance time of dye	1 45/60 minutes	1 45/60 minutes
Total excretion of dye	14 per cent.	14 per cent.
Prussian blue period:		
Amount of urine, fourth hour	30 c.c.	30 c.c.
Appearance time of dye	1 minute	1 minute
Total excretion of dye	22 per cent.	20 per cent (?)

* All dyes were given intravenously.

EXPERIMENT 6.—Dog 25, weight 7.5 kg. Anesthetized with paraldehyd. Double lumbar incision followed by ureteral catheterization. Diuresis induced by 200 c.c. of water by stomach-tube and by intravenous injection of 10 per cent. saline solution. At necropsy the two kidneys were of equal weight and appeared normal. No abnormal histological changes were found.

TABLE 4.—FINDINGS IN EXPERIMENT 6

	Right Kidney	Left Kidney
Amount of urine, first hour	27 c.c.	21 c.c.
Specific gravity	1.017	1.012
Sodium chlorid per 100 c.c.	.80 gm.	.84 gm.
Total chlorid	216 mg.	176 mg.
Nitrogen per 100 c.c.	.30 gm.	.39 gm.
Total nitrogen	81 mg.	82 mg.
Diastase before diuresis	32	32
Diastase after diuresis	15	15
Freezing-point	—.910°	—1.03°
Hydrogen ionization	7.4	7.0
Phenolsulphonephthalein period:*		
Amount of urine, second hour	16 c.c.	16 c.c.
Appearance time of dye	2 minutes	2 minutes
Total excretion of dye	19 per cent.	15 per cent.
Indigocarmin period:		
Amount of urine, third hour	27 c.c.	25 c.c.
Appearance time of dye	2½ minutes	2½ minutes
Total excretion of dye	21 per cent.	20 per cent.
Prussian blue period:		
Amount of urine, fourth hour	35 c.c.	35 c.c.
Appearance time of dye	1¾ minutes	1¾ minutes
Total excretion of dye		†

* All dyes were given intravenously. There was leakage of phenolsulphonephthalein at the point of injection.

† Left kidney excreted 10 per cent. more than the right kidney. Accurate estimation impossible on account of difference in color.

These three experiments show that under the conditions stated the amount of urine normally excreted from hour to hour from the two kidneys was nearly identical. There was considerable variation in both the concentration and total output of chlorid and nitrogen, and, as a result, variation in the molecular concentration as determined by the freezing-point. The amount of diastase from the two sides was the same. Dilution of urine by diuresis had a marked effect on the excretion of this ferment, as was to be expected from Wohlgemuth's and Geraghty, Rowntree and Carey's studies. The acidity of the urine showed only slight differences. The dye substances were all excreted promptly and in corresponding amounts from the two sides. As pointed out by Goodman and Kristeller and by Thomas, the total excretion of indigocarmin was approximately one-half that of phenolsulphonephthalein. The difficulty of quantitating the excretion of potassium ferrocyanid is illustrated by the last two experiments. There is no reason to believe that the amounts excreted from the two sides were different. Yet the precipitate from one kidney was blue and from the other green. Comparative color readings, therefore, were very inaccurate.

GROUP 2: ANIMALS WITH WELL-MARKED NEPHRITIS

EXPERIMENT 7.—Dog 17, weight 9.6 kg.; 0.8 mg. of uranium nitrate (0.085 mg. per kilogram body weight) injected into left renal artery according to

TABLE 5.—FINDINGS IN EXPERIMENT 7

	Right Kidney	Left Kidney
Amount of urine, first hour	10 c.c.	15 c.c.
Specific gravity	1.039	1.015
Sodium chlorid per 100 c.c.	1.6 gm.	1.1 gm.
Total chlorid	160 mg.	165 mg.
Nitrogen per 100 c.c.	2.00 gm.	.42 gm.
Total nitrogen	200 mg.	63 mg.
Diastase before diuresis	400	62.5
Freezing-point	—3.09°	—1.00°
Hydrogen ionization	5.5	8.00
Phenolsulphonephthalein period:*		
Amount of urine, second hour	12 c.c.	61 c.c.
Appearance time of dye	6 minutes	5 minutes
Total excretion of dye	50 per cent.	30 per cent.
Indigocarmin period:		
Amount of urine, third hour	8 c.c.	15 c.c.
Appearance time of dye	†	†
Total excretion of dye	20 per cent.	13 per cent.
Prussian blue period:		
Amount of urine, fourth hour	16 c.c.	35 c.c.
Appearance time of dye	4 minutes	2 minutes
Total excretion of dye	.....	‡

* All dyes were given intravenously. There was leakage of phenolsulphonephthalein around the point of injection, so when the color first appeared in the urine a second injection was given. Prussian blue in both urines precipitated as a green sediment which could not be read against the standard solution. The two urines, therefore, were compared against each other.

† Identical on both sides.

‡ The left kidney excreted 66 per cent. as much as the right.

method described. Forty-eight hours later anesthetized with paraldehyd. Ureters catheterized after exposure through double lumbar incision. Diuresis induced by 200 c.c. of water by stomach-tube and by intravenous injections of 10 per cent. saline solution. At necropsy, the right kidney was normal. The left kidney was much enlarged, firm, and dark. Microscopic sections from the right kidney, normal. Sections from the left kidney show no glomerular lesions, but marked tubular destruction.

EXPERIMENT 8.—Dog 9, weight 6.2 kg.; 0.6 mg. of uranium nitrate (0.1 mg. per kilogram body weight) injected into left renal artery according to the method described. After seventy-two hours, anesthetized with paraldehyd. Ureteral catheterization. Diuresis induced by 200 c.c. of water by stomach-tube and by intravenous injections of 10 per cent. saline solution. At necropsy, both kidneys looked normal. Microscopic sections from the right kidney were not remarkable. Sections from the left kidney showed no glomerular lesions, but marked tubular destruction.

TABLE 6.—FINDINGS IN EXPERIMENT 8

	Right Kidney	Left Kidney
Amount of urine, first hour	38 c.c.	4 c.c.
Sodium chlorid per 100 c.c.	.5 gm.	.8 gm.
Total chlorid	190 mg.	32 mg.
Nitrogen per 100 c.c.	1.00 gm.	.01 gm.
Total nitrogen	380 mg.	4 mg.
Phenolsulphonephthalein:*		
Appearance time of dye	6 minutes	29 minutes
Total excretion	20 per cent.	Traces

* The dye was given intramuscularly.

TABLE 7.—FINDINGS IN EXPERIMENT 9

	Right Kidney	Left Kidney
Amount of urine, first hour	45 c.c.	4.4 c.c.
Specific gravity	1.014	1.006
Sodium chlorid per 100 c.c.	1.5 gm.	1.2 gm.
Total chlorid	675 mg.	52 mg.
Nitrogen per 100 c.c.	.31 gm.	.08 gm.
Total nitrogen	139 mg.	3 mg.
Diastase before diuresis	62.5	
Diastase after diuresis	32	16
Freezing-point	—1.08°	—.7°
Phenolsulphonephthalein period:*		
Amount of urine	40 c.c.	3 c.c.
Appearance time of dye	2 minutes	5 minutes
Total excretion of dye	54 per cent.	Traces

* Dye given intravenously.

EXPERIMENT 9.—Dog 24, weight 4.2 kg.; 0.5 mg. of uranium nitrate (0.12 mg. per kilogram body weight) injected into the left renal artery according to the method described. Two and one-half weeks later the animal was anesthetized with paraldehyd and the ureters were catheterized. Diuresis was induced by 200 c.c. of water by stomach-tube and by intravenous injections of 10 per cent. saline solution. At necropsy, the right kidney weighed 24 gm. and was normal. The left kidney weighed 17 gm., was of firm consistency and pale. The cortex was narrowed, and the kidney markings were obscured. The capsule was stripped with difficulty. Sections from the right kidney were not remarkable. Sections from the left kidney showed a considerable formation

of scar tissue. Many of the glomeruli were completely destroyed and sclerosed. In parts of the kidney, however, they were less severely damaged and showed the remains of glomerular epithelium with old fibrinous thrombi in the capillaries. In areas through the kidney, no tubular epithelium was left. Here the lumen of the tubules was filled with necrotic material and serum. In other places there was evidence of tubular regeneration as shown by large atypical epithelium. Throughout the entire kidney there was considerable edema.

EXPERIMENT 10.—Dog 18, weight 11.1 kg.; 0.8 mg. of uranium nitrate (0.07 mg. per kilogram body weight) injected into the left renal artery according to the method described. Twenty-four hours later anesthetized with paraldehyd. Ureteral catheterization. Diuresis induced by 200 c.c. of water by stomach-tube and by intravenous injections of 10 per cent. saline solution. At necropsy the right kidney appeared normal. The left kidney was enlarged, congested, and showed numerous small areas of necrosis. Microscopic sections from the right kidney were normal. Sections from the left kidney showed a few necrotic glomeruli, others, with fibrinous thrombi in the glomerular capillaries, and others with edema and hemorrhage into the subcapsular space. The majority of the glomeruli, however, showed no lesions. The tubules throughout the entire kidney were markedly damaged.

TABLE 8.—FINDINGS IN EXPERIMENT 10

	Right Kidney	Left Kidney
Amount of urine, first hour	65 c.c.	4 c.c.
Specific gravity	1.020	1.012
Sodium chlorid per 100 c.c.	1.5 gm.	1.00 gm.
Total chlorid	975 mg.	40 mg.
Nitrogen per 100 c.c.	.70 gm.	.02 gm.
Total nitrogen	455 mg.	.8 mg. (?)
Diastase before diuresis	500	80
Diastase after diuresis	32	16
Freezing-point	—1.5°	—.5°
Hydrogen ionization	8.00	8.7
Phenolsulphonephthalein period:*		
Amount of urine, second hour	70 c.c.	4 c.c.
Appearance time of dye	1½ minutes	14 minutes
Total excretion of dye	61 per cent.	Traces
Indigocarmin period:		
Amount of urine, third hour	30 c.c.	7 c.c.
Appearance time of dye	2 minutes	14 minutes
Total excretion of dye	38 per cent.	Traces
Prussian blue period:		
Amount of urine, fourth hour	40 c.c.	4 c.c.
Appearance time of dye	1¼ minutes	21 minutes
Total excretion of dye	50 per cent.	Traces

* All dyes were given intravenously.

EXPERIMENT 11.—Dog 22, weight 13.8 kg.; 1.8 mg. of uranium nitrate (0.13 mg. per kilogram body weight) injected into the left renal artery according to the method described. After twenty-four hours, anesthetized with paraldehyd. Ureteral catheterization. Diuresis induced by 200 c.c. of water by stomach-tube, and by intravenous injections of 10 per cent. saline solution. At necropsy, the right kidney was normal; the left kidney was enlarged, dark red in color and of firm consistency. Sections from the right kidney were normal. Sections from the left kidney showed marked hemorrhagic necrosis destroying both tubules and glomeruli.

TABLE 9.—Findings in Experiment 11

	Right Kidney	Left Kidney
Amount of urine, first hour	40 c.c. in 1 hr.	1.6 c.c. in 4 hrs.
Specific gravity	1.018	1.015
Sodium chlorid per 100 c.c.	1.2 gm.	1.6 gm.
Total chlorid	480 mg.	25 mg.
Diastase before diuresis	32	
Diastase after diuresis	16	32
Freezing-point	—1.17°	—.62°
Hydrogen ionization	Acid to phthalein	Alkaline to phthalein
Phenolsulphonephthalein period:*		
Amount of urine, second hour	40 c.c.	
Appearance time of dye	1¼ minutes	None in 1 hour
Total excretion of dye	49 per cent.	
Indigocarmin period:		
Amount of urine, third hour	40 c.c.	
Appearance time of dye	1¼ minutes	None in 1 hour
Prussian blue period:		
Amount of urine, fourth hour	40 c.c.	
Appearance time of dye	1½ minutes	None in 1 hour
Total excretion	68 per cent.	

*All dyes were given intravenously. It was impossible to determine the indigocarmin excretion quantitatively. The urine from the affected kidney contained considerable blood.

TABLE 10.—Findings in Experiment 12

	Right Kidney	Left Kidney
Amount of urine, first hour	35 c.c.	.4 c.c. in 4 hrs.
Specific gravity	1.018	1.011
Sodium chlorid per 100 c.c.	1.2 gm.	.9 gm.
Total chlorid	420 mg.	Traces
Nitrogen per 100 c.c.	.28 gm.	Traces
Notal nitrogen	98 mg.	
Diastase before diuresis	500	
Diastase after diuresis	32	Not determined
Freezing-point	—1.60°	Nearly zero
Phenolsulphonephthalein period:*		
Amount of urine, second hour	50 c.c.	
Appearance time of dye	2½ minutes	
Total excretion of dye	46 per cent.	None excreted
Indigocarmin period:		
Amount of urine, third hour	18 c.c.	
Appearance time of dye	2 minutes	
Total excretion of dye	15 per cent.	None excreted
Prussian blue period:		
Amount of urine, fourth hour	80 c.c.	
Appearance time of dye	2½ minutes	
Total excretion of dye	52 per cent.	None excreted

*All dyes were injected intravenously. The Prussian blue reading is inaccurate on account of color changes.

Experiment 12.—Dog 23, weight 10.3 kg.; 1 mg. of uranium nitrate (0.1 mg. per kilogram body weight) injected into the left renal artery according to the method described. Ninety-six hours later, anesthetized with paraldehyd, and ureters catheterized. Diuresis induced by 200 c.c. of water by stomach-tube and by intravenous injections of 10 per cent. saline solution. At necropsy, the right kidney was normal. The left kidney was enlarged and markedly congested. Sections from the left kidney showed areas of hemorrhagic necrosis in which

both tubules and glomeruli were destroyed. In the greater part of the kidney, the glomeruli were severely damaged. The tubules throughout were filled with cells, serum or necrotic material. The lining epithelium when present was atypical.

EXPERIMENT 13.—Dog 12, weight 11.4 kg.; 0.8 mg. of uranium nitrate (0.07 mg. per kilogram body weight) injected into the left renal artery according to the method described. After forty-eight hours, anesthetized with paraldehyd. Ureteral catheterization. Diuresis induced by 200 c.c. of water by stomach-tube and by intravenous injections of 10 per cent. saline solution. At necropsy, the right kidney was normal. The left kidney was much enlarged, dark, and contained scattered areas of necrosis. Microscopic sections from the right kidney were normal. Sections from the left kidney showed a few areas where the glomeruli and tubules were but little damaged. The greater part of the kidney, however, showed acute degenerative changes involving both glomeruli and tubules.

TABLE 11.—FINDINGS IN EXPERIMENT 13

	Right Kidney	Left Kidney
Amount of urine, first hour	48 c.c.	
Specific gravity	1.019	
Sodium chlorid per 100 c.c.	.94 gm.	
Total chlorid	481 mg.	
Nitrogen per 100 c.c.	.94 gm.	
Total nitrogen	481 mg.	The left kidney
Diastase after diuresis	.32	was anuric
Freezing-point	—1.65°	during the
Hydrogen ionization	8.4	entire period
Phenolsulphonephthalein period:*		of observation.
Appearance time of dye	5 minutes	
Total excretion of dye	38 per cent.	
Indigocarmin period:		
Appearance time of dye	2 minutes	
Prussian blue period:		
Appearance time of dye	1½ minutes	
Total excretion of dye	42 per cent.	

* Phenolsulphonephthalein and indigocarmin injected intramuscularly. Indigocarmin gave a greenish color to the urine which was impossible to estimate quantitatively.

These experiments illustrate several of the features which have been discovered in clinical studies on renal function. The amount of urine excreted from the two sides showed marked variations. In the least severe type of nephritis, more urine appeared from the diseased side than from the control kidney. As the lesion progressed the kidney became less able to excrete fluid, and finally became anuric. The specific gravity of the urine from the diseased kidney was always less than from the normal side and had no relation, therefore, to the total fluid excretion. The concentration of sodium chlorid seemed to have no definite relation to the severity of the lesion. In four experiments, it was lower in the pathological kidney's urine than in the control's, but in two cases was higher. The total excretion, however, tended to diminish with an increasing disease. The concentration and total output of nitrogen was a better index of renal function. Both diminished

strikingly in proportion to the severity of anatomical changes found in the kidney. As the disease progressed, differences in the molecular concentration of the urine increased. As a result, the freezing-point of the urine from the affected side was nearer zero.

The diastase readings are of particular interest. In the two cases in which the determinations were made before diuresis was induced, differences were found which appeared to point out differences in degree of disease. After diuresis, however, the test was of little value. In Dog 4 the diastase reading was higher on the diseased side than on the control side, and equaled the output obtained before sodium chlorid was injected. The dog was practically anuric, and had a marked hematuria. This probably accounts for the atypical finding. In the three cases tested, there was a slight change in the hydrogen ionization of the urine from the diseased side. In two cases it was marked; in one, it was no greater than in the control series. It seems warrantable to believe, however, that in unilateral nephritis the markedly diseased kidney tends to excrete a less acid urine than normal.

The total excretion of the three dye substances was much alike and depended on the severity of the lesion. Potassium ferrocyanid and phenolsulphonephthalein were excreted with nearly equal rapidity, while indigocarmin was much less completely eliminated. The first experiment illustrates that the appearance time of a dye in the urine may give misleading information. In this animal the diseased kidney put out more urine than the normal, and the dyes from the injured side came to the urine as soon as from the control side or even sooner, although the total excretion was considerably less. In the more advanced cases, the appearance time of all the dyes from the diseased side was delayed in proportion to the severity of the lesion.

Therefore, these experiments showed that with an increasingly severe nephritis, the urine from the affected side became more dilute. The excretion of nitrogen diminished in proportion to the severity of the lesion. The excretion of chlorid was more variable. Differences in the freezing-point of the compared urines showed the diseased side and, in a general way, afforded a quantitative test for the function of the two kidneys. This determination, however, was not so accurate a test for renal function as the comparative output of nitrogen or dyes.

The excretion of the three dyes which were used afforded a good index of disturbed function. Phenolsulphonephthalein was eliminated more completely and was simpler to estimate quantitatively than indigocarmin or potassium ferrocyanid. The excretion of diastase gave valuable information in regard to the degree of renal injury except when there were marked differences in the amount of urine which came from the two kidneys.

GROUP 3: ANIMALS WITHOUT NEPHRITIS BUT WITH ABNORMAL RENAL FUNCTION

EXPERIMENT 14.—Dog 14, weight 10.5 kg.; 0.6 mg. of uranium nitrate (0.06 mg. per kilogram body weight) injected into the left renal artery according to the method described. After twenty-four hours, anesthetized with paraldehyd.

TABLE 12.—FINDINGS IN EXPERIMENT 14

	Right Kidney	Left Kidney
Amount of urine, first hour	20 c.c.	25 c.c.
Specific gravity	1.032	1.034
Sodium chlorid per 100 c.c.	.74 gm.	.86 gm.
Total chlorid	148 mg.	215 mg.
Nitrogen per 100 c.c.	.63 gm.	.50 gm.
Total nitrogen	126 mg.	125 mg.
Diastase after diuresis	62.5	32
Freezing-point	—1.72°	—1.56°
Hydrogen ionization	7.8	7.8
Phenolsulphonephthalein period:*		
Amount of urine, second hour	15 c.c.	22 c.c.
Appearance time of dye	2½ minutes	6 minutes
Total excretion	15 per cent.	16 per cent.
Indigocarmin period:		
Amount of urine, third hour	17 c.c.	
Appearance time of dye	10 minutes	15 minutes
Prussian blue period:		
Amount of urine, fourth hour	12 c.c.	17 c.c.
Appearance time of dye	†	‡
Total excretion time of dye		

* Phenolsulphonephthalein and indigocarmin were given intramuscularly. It was impossible to quantitate the indigocarmin excretion.

† Slightly sooner from the right than from the left.

‡ Left kidney excreted 10 per cent. more than the right.

TABLE 13.—FINDINGS IN EXPERIMENT 15

	Right Kidney	Left Kidney
Amount of urine, first hour	23 c.c.	33 c.c.
Specific gravity	1.012	1.008
Sodium chlorid per 100 c.c.	1.5 gm.	1.2 gm.
Total chlorid	345 mg.	396 mg.
Nitrogen per 100 c.c.	.44 gm.	.32 gm.
Total nitrogen	101 mg.	106 mg.
Diastase after diuresis	24	16
Freezing-point	—1.45°	—1.05°
Hydrogen ionization	8.3	8.3
Phenolsulphonephthalein period:*		
Amount of urine, second hour	50 c.c.	60 c.c.
Appearance time of dye	1 minute	1 minute
Total excretion of dye	51 per cent.	45 per cent.
Indigocarmin period:		
Amount of urine, third hour	14 c.c.	20 c.c.
Appearance time of dye	1 minute	1 minute
Total excretion of dye	25 per cent.	25 per cent.
Prussian blue period:		
Amount of urine, fourth hour	17 c.c.	18 c.c.
Appearance of dye	1 minute	1 minute
Total excretion of dye		†

* All dyes were given intravenously.

† Left kidney excreted 10 per cent. more than the right.

Ureteral catheterization. Diuresis induced by 200 c.c. of water by stomach-tube, and by intravenous injections of 10 per cent. saline solution. At necropsy the two kidneys appeared normal and were of equal weight. Sections from the left kidney showed no evidence of an acute lesion.

EXPERIMENT 15.—Dog 16, weight 7.6 kg.; 1 c.c. of normal salt solution was injected into the left renal artery according to the method described. Twenty-four hours later the animal was anesthetized with paraldehyd. Ureteral catheterization. Diuresis induced by 200 c.c. of water by stomach-tube, and by intravenous injections of 10 per cent. saline solution. At necropsy the two kidneys appeared normal and were of equal weight. Sections from the left kidney showed no evidence of an acute lesion.

EXPERIMENT 16.—Dog 19, weight 10 kg.; 0.9 mg. of uranium nitrate (0.08 mg. per kilogram body weight) injected into the left renal artery according to the method described. There was slight leakage at the point of injection. After forty-eight hours, anesthetized with paraldehyd. Ureteral catheterization. Diuresis induced by 200 c.c. of water by stomach-tube, and by intravenous injection of 10 per cent. saline solution. At necropsy the two kidneys were of equal weight and appeared normal. Microscopic sections from the right kidney were negative. Sections from the left kidney were not remarkable except for a few foci of round-cell infiltration. There was no evidence of any acute lesion.

TABLE 14.—FINDINGS IN EXPERIMENT 16

	Right Kidney	Left Kidney
Amount of urine, first hour	15 c.c.	30 c.c.
Specific gravity	1.007	1.004
Sodium chlorid per 100 c.c.	1.24 gm.	1.5 gm.
Total chlorid	186 mg.	450 mg.
Nitrogen per 100 c.c.	.43 gm.	.27 gm.
Total nitrogen	64 mg.	81 mg.
Diastase before diuresis	64	64
Diastase after diuresis	8	8
Freezing-point	—1.63°	—1.33°
Hydrogen ionization	7.8	7.8
Phenolsulphonephthalein period:*		
Amount of urine, second hour	20 c.c.	50 c.c.
Appearance time of dye	1½ minutes	1½ minutes
Total excretion of dye	35 per cent.	38 per cent.
Indigo carmin period:		
Appearance time of dye	2 minutes	2 minutes
Total excretion of dye	24 per cent.	26 per cent.
Prussian blue period:		
Amount of urine, fourth hour	20 c.c.	50 c.c.
Appearance time of dye	1¼ minutes	1⅓ minutes

* All dyes were given intravenously. It was impossible to estimate either the total or comparative output of potassium ferrocyanid on account of differences in color.

EXPERIMENT 17.—Dog 15, weight 9.6 kg.; 0.6 mg. of uranium nitrate (0.06 mg. per kilogram body weight) injected into the left renal artery according to the method described. Five days later anesthetized with paraldehyd. Ureteral catheterization. Diuresis induced by 200 c.c. of water by stomach-tube, and by intravenous injections of 10 per cent. saline solution. At necropsy, the two kidneys were of equal weight and appeared normal. No abnormal histological changes were found.

EXPERIMENT 18.—Dog 26, weight 7.2 kg. The left kidney was exposed and handled as usual without injection of the renal artery. Twenty-four hours later the animal was anesthetized with paraldehyd and the ureters were catheterized. Diuresis was induced by 200 c.c. of water by stomach-tube and by intravenous

injections of 10 per cent. saline solution. At necropsy, the two kidneys were of equal weight and appeared normal. Nothing abnormal was found in either kidney by histological examination.

TABLE 15.—FINDINGS IN EXPERIMENT 17

	Right Kidney	Left Kidney
Amount of urine, first hour	16 c.c.	45 c.c.
Specific gravity	1.033	1.015
Sodium chlorid per 100 c.c.	.60 gm.	1.00 gm.
Total chlorid	96 mg.	450 mg.
Nitrogen per 100 c.c.	.46 gm.	.31 gm.
Total nitrogen	73 mg.	139 mg.
Diastase after diuresis	64	32
Freezing-point	—2.31°	—2.00°
Hydrogen ionization	8.0	5.5
Phenolsulphonephthalein period:*		
Amount of urine, second hour	15 c.c.	45 c.c.
Appearance time of dye	4 minutes	4¼ minutes
Total excretion of dye	30 per cent.	35 per cent.
Indigocarmin period:		
Amount of urine, third hour	22 c.c.	45 c.c.
Appearance time of dye	†	†
Total excretion of dye	18 per cent.	18 per cent.
Prussian blue period:		
Amount of urine, fourth hour	12 c.c.	32 c.c.
Appearance time of dye	‡	‡
Total excretion of dye		

* Phenolsulphonephthalein and indigocarmin were given intramuscularly. It was impossible to determine accurately the relative or absolute amounts of potassium ferrocyanid excreted on account of color changes.

† Identical on both sides.

‡ Slightly sooner from the right kidney than from the left. Left kidney excreted considerably more than the right.

TABLE 16.—FINDINGS IN EXPERIMENT 18

	Right Kidney	Left Kidney
Amount of urine, first hour	18 c.c.	65 c.c.
Specific gravity	1.017	1.012
Sodium chlorid per 100 c.c.	1.6 gm.	1.3 gm.
Total chlorid	288 mg.	845 mg.
Nitrogen per 100 c.c.	.62 gm.	.22 gm.
Total nitrogen	117 mg.	143 mg.
Diastase before diuresis	32	16
Diastase after diuresis	4	3
Freezing-point	—1.35°	—.85°
Hydrogen ionization	7.4	7.0
Phenolsulphonephthalein period:		
Amount of urine, second hour	16 c.c.	38 c.c.
Appearance time of dye	2½ minutes	2 minutes
Total excretion of dye	40 per cent.	42 per cent.
Indigocarmin period:		
Amount of urine, third hour	25 c.c.	31 c.c.
Appearance time of dye	1¾ minutes	1¾ minutes
Total excretion of dye	20 per cent.	20 per cent.
Prussian blue period:		
Amount of urine, fourth hour	42 c.c.	61 c.c.
Appearance time of dye	2 minutes	1½ minutes
Total excretion of dye	.....	*

* Left kidney excreted nearly twice as much as right. Accurate estimation impossible on account of differences in color.

The striking feature in the last series of experiments was the pronounced polyuria occurring from the side which had been manipulated. It occurred during each of the four hours of observation and so cannot be attributed to a normal variation in the amount of urine excreted. The specific gravity of the urine from the polyuric kidney was always the lower. Both the concentration of sodium chlorid and its total output varied widely. But in every instance, the total output of sodium chlorid from the abnormal side was greater than from the control side. The concentration of nitrogen from the diseased kidney was lower in every case than from the normal kidney. The total output for the period, however, was considerably highly than on the control side. In every case, the freezing-point was lower in the normal urine than in the urine from the polyuric kidney, which showed that the kidney with polyuria secreted a urine of less molecular concentration than normal. As might be expected from the previous notes, the diastase readings were insignificant. In two cases, the reaction of the urine was more acid from the diseased side than from the control. In the other cases the hydrogen ionization of the two urines was the same. As in the preceding experiments, the excretion of dyes from the two kidneys was parallel. In the case with the least polyuria, the appearance time of all the dyes from the affected kidney was delayed. In the remaining experiments, the dyes appeared in the two urines at approximately the same time. The total amount of dye excreted from the two kidneys in each instance was nearly the same. In certain of the experiments one or another dye appeared to be excreted from the diseased side in an amount above normal.

Thus, these experiments are radically different from those observations in which the kidney was definitely diseased. Here the amount of urine, nitrogen and chlorid which was excreted from the injured kidney was greater than from the control side, and the amount of dyes put out was at least normal. The explanation of these findings is uncertain. Further studies in this condition are necessary to understand its significance.

SUMMARY

Experiments have been undertaken to compare, on the same animal, the tests for renal function which are most commonly used in studying unilateral disease. Nephritis was produced by the injection of uranium nitrate into the renal artery of one kidney, according to the method of Ribbert and Baehr. By this procedure, one-sided lesions of varying intensity were caused.

The results of these experiments fall into two groups. One group consists of animals whose kidneys anatomically were normal yet functionally were pathological. The functional condition encountered suggested a hyperpermeability of the kidney to water, chlorid, nitrogen

and in certain instances, to various dyes. No explanation for these findings is offered.

The other group of experiments consists of animals in which a well-marked nephritis was produced. In these animals, tests for renal function were applied and gave results similar to those which have been reported in human beings.

Clinical studies have suggested that a close parallelism exists between the degree of kidney destruction and the kidney's ability to excrete various solid substances; and that all the tests most commonly used in the study of renal function give parallel results. The experiments reported demonstrate by a variety of tests for renal function made on the same animal at the same time that such a parallelism does exist, but that certain of the tests are more significant than others.

The total excretion of nitrogen from one kidney over a given period of time, as compared with its excretion from the other kidney, gives accurate information in regard to the existence and degree of disease. The comparative excretion of diastase from the two kidneys is a valuable test for renal function when the amount of urine from the two kidneys is nearly the same. This test has a striking disadvantage. Dilution of urine produces such marked differences in the diastase excretion that when the urine from the two kidneys is excreted in different amounts the observation becomes valueless. As the renal disease advances and the urine becomes more dilute, the freezing-point approaches zero. This determination, however, is not so sharp a quantitative test for renal function as the excretion of nitrogen or dye substances.

Of the two dyes commonly used, phenolsulphonephthalein is the better. It can be injected in small bulk, is excreted rapidly from the kidneys, and the amount put out can be quantitated accurately. Indigocarmin does not show changes in renal function which are not demonstrated by phenolsulphonephthalein, and has two disadvantages. It requires a considerable amount of injection fluid and its excretion is difficult to read colorimetrically. The latter objection can be obviated, in part, by intravenous administration of the dye. The excretion of potassium ferrocyanid parallels that of phenolsulphonephthalein and indigocarmin, but is more difficult to estimate colorimetrically. Hence, for practical purposes, it is of no value as a test for renal function. The reaction of the urine from a severely diseased kidney apparently tends to become less acid than that from the normal side. This variation, however, is not sufficiently marked to be used as a functional test for one-sided disease.

It appears, therefore, from the foregoing experimental observations, that renal function is best estimated by the determination of nitrogen excretion and by the phenolsulphonephthalein test.

STUDIES IN PAROXYSMAL EDEMA*

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Recently two cases with histories of periodic attacks of generalized edema without the usual evidence of kidney disease have been under observation in the Massachusetts General Hospital. These seem, together with certain chemical investigations on them, to be of sufficient interest to be reported.

CASE 1.—*History.* Mrs. D., aged 33, in excellent circumstances, at an early age was operated on for acute appendicitis. Since this operation a previous troublesome constipation has been more marked. In 1909, at the end of her last pregnancy, she was seriously ill with the kidney of pregnancy. During this time there appeared in the urine large amounts of albumin and casts which gradually disappeared after the birth of the child. For the past three or four years she has been engaged actively in social and philanthropic interests.

In June, 1913, the patient came to Dr. Edsall for the first time, complaining of attacks of prostration, associated with nausea, which passed off after rest. At other times she has attacks in which there is a generalized edema resulting in a gain of as much as 15 pounds in weight. The edema rapidly passes off as soon as free catharsis is established. Accompanying the edema the only symptom is an unpleasant feeling of tenseness of the skin. The attacks of edema are prone to occur when she becomes constipated, and are said to bear some relation to menstruation.

Physical Examination.—The physical examination is negative. Repeated examination of the urine failed to reveal casts or albumin.

Management.—Inability of the kidney to excrete chlorids was suspected of being the cause of the attacks of edema and in July the patient was put on a diet low in salt. Since she has been on this diet she has had no attacks similar to those previously described, except on one occasion when additional salt was given to test the functional capacity of the kidney for salt excretion. On four different occasions in October and November her daily excretion of sodium chlorid was determined and was between 2 and 3 grams. In December on two successive days she was given 6 grams additional salt with the result that on those days her twenty-four-hour amount of sodium chlorid excretion was only 0.32 gm. on the first, and 0.75 gm. on the second day. Accompanying the ingestion of the salt there was nausea and edema, which disappeared as soon as free catharsis was established. More extensive and accurate chemical studies were impossible because the patient was not in the hospital.

CASE 2.—*History.*—The second case, a Russian Jew, aged 40, was on the recommendation of Dr. J. H. Pratt, admitted to the East Medical Service of the Massachusetts General Hospital, Feb. 24, 1914, complaining of cough, dyspnea and swelling of the face, body and extremities.

Family History.—Not remarkable.

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* From the Medical Service and the Chemical Laboratory of the Massachusetts General Hospital.

* An abstract of this paper was presented at the meeting of the American Association for the Advancement of Clinical Research, Atlantic City, May, 1914.

Past History.—The patient had measles in childhood and bronchitis ten years ago; otherwise has considered himself well. He is habitually constipated. He has not had tonsillitis, rheumatism or scarlet fever and denies veneral disease. He does not use tea, coffee, alcohol or tobacco excessively. His work is selling salt fish, which requires no great exertion, but much walking.

Present Illness.—Six years ago he first noticed swelling of the scrotum associated with a slight dry cough, but no dyspnea, or swelling of the legs. After two weeks' rest the swelling of his testicles disappeared and the cough ceased.

A year later, five years ago, there was a return of the edema of the scrotum with edema of the legs, abdomen, chest and face, associated with some shortness of breath. A similar attack has occurred each year, and each time has passed off after a two weeks' rest.

For the past six months he has had varying degrees of edema of the face, abdomen and legs, and moderate dyspnea. During the past week both the edema and the dyspnea have increased. He has had no orthopnea, but is subject to choking attacks in which he gets blue in the face. His urine is scanty.

Physical Examination.—This shows a man of medium height able to lie flat in bed without discomfort, breathing noisily but not rapidly. The face is markedly edematous, the puffiness about the eyes nearly closing them. The skin, sclerae, mucosae and lymph-nodes reveal nothing abnormal. The pupils are equal, regular and react normally. The tongue, throat and tonsils are generally reddened. There is marked pyorrhea alveolaris. The heart's impulse is neither seen nor felt at the apex; the left border of cardiac dulness on percussion is 13 cm. to the left, the right border 3 cm. to the right of the midsternal line. The heart sounds are regular and of good quality. There is heard over the precordia a cardiorespiratory murmur. The pulmonic second sound is louder than the aortic and is accentuated. The pulses are of good volume and tension. The artery walls are easily palpable and distinctly thickened. Nothing is found in the lungs. There is shifting dulness in the abdomen, but no fluid wave can be made out. Neither spleen nor liver is felt, no masses or tenderness discovered. There is a marked soft edema of the abdominal wall, of the penis and scrotum and a massive brawny edema of the legs and thighs.

The Wassermann reaction on the blood is negative. The urine on repeated examinations showed no albumin or anything abnormal in the sediment.

Clinical Course.—He was kept in bed, given no drugs and put on a salt-low diet. The remarkable diuresis, loss of weight and diminishing edema is best appreciated by consulting the accompanying table. In five or six days he reached what may be assumed to be his normal weight. All subjective symptoms cleared rapidly with the loss of edema and he was soon up about the ward without dyspnea or any return of the edema. Dr. J. H. Pratt made daily observations on the blood-pressure and heart condition.

March 3. The apex is noted as being in the sixth space, visible and easily palpable, 14 cm. outside the midsternal line.

March 5. Orthodiagram by Dr. Holmes shows the heart shadow enlarged to the left and lying somewhat horizontal in the chest. The apex is in the sixth space, 10 cm. to the left of the median line. The right border is 8 cm. to the right of the median line. The total transverse diameter is 18 cm.

March 17. The apex impulse is visible and palpable in the fifth space, 10 cm. from the median line. Sounds are loud and clear.

The systolic blood-pressure at entrance was 150 mm. where it remained for seven days, then falling to 115 mm. where it stayed while the patient remained in the hospital. The diastolic was 115 mm. at entrance and constant for eight days, then becoming 100 mm., did not change until the patient left the hospital.

In the second case the periodicity and degree of edema without evidence of kidney disease as determined by the usual clinical examina-

tion, and a history of circulatory disturbance not of sufficient severity to explain the condition satisfactorily, suggested more careful studies of the functional activities of the kidney. Accordingly the following observations were made.

1. Urinary output and specific gravity.

2. The urinary acidity (hydrogen ion concentration) as estimated by Henderson and Palmer.[1]

3. Titratable acid of the urine as described by Henderson.[2]

4. Urinary ammonia, Folin's new method.[3]

5. Chlorids, Volhard's method.

6. Phenolsulphonephthalein excretion as described by Rowntree and Garaghty.[4]

7. Salt, lactose and potassium iodid excretion was determined as recommended by Schlayer.[5]

The urinary nitrogen was also determined, but as the patient's diet was not analyzed the nitrogen balance is only approximate.

DISCUSSION

Bohne[6] in 1897 first recognized reduced excretion of chlorids in cases with edema and later, in 1902, Widal[7] and Strauss[8] pointed out the important relation between edema and sodium chlorid retention in connection with therapeutic measures in these cases. So much literature on the subject has accumulated that it is impossible in a brief report of this nature to review critically the experimental and clinical facts on sodium chlorid metabolism brought to light in the various papers. Excellent reviews have been made by von Noorden,[9] Chris-

1. Henderson, L. J., and Palmer, W. W.: The Intensity of Urinary Acidity in Normal and Pathological Conditions, Jour. Biol. Chem., 1913, xiii, 393.

2. Henderson, L. J.: The Process of Acid Excretion, Jour. Biol. Chem., 1911, ix, 403.

3. Folin, O., and MacCallum, A. B.: The Determination of Ammonia in Urine, Jour. Biol. Chem., 1912, xi, 523.

4. Rowntree, L. G., and Geraghty, J. T.: An Experimental and Clinical Study of Phenolsulphonephthalein in Relation to Renal Function in Health and Disease, THE ARCHIVES INT. MED., 1912, ix, 284.

5. Schlayer and Takayasu: Untersuchungen über die Funktion kranker Nieren beim Menschen, Deutsch. Arch. f. klin. Med., 1910-11, ci, 333.

6. Bohne, J.: Ueber die Bedeutung der Retention von Chloriden im organismus für die Entstehung urämischer und comatöser Zuständ, Fortschr. d. Med., 1897, xv, 121.

7. Widal, F.: La cure de déchlorination, Bull. méd. d. hôp., Paris, 1903, xx, 773, 990.

8. Strauss, H.: Zur Behandlung und Verhütung der Nierenwassersucht, Therap. d. Gegenw., 1902, iv, 444; 1903, v, 193.

9. von Noorden, C.: Metabolism and Practical Medicine, English translation. 1907, ii, 461, Chicago.

TABLE GIVING DATA OF METABOLISM—

Date Feb.	Fluid Intake	Urine, c.c.	Sp. Gr.	Total Solids	+ * H	Acid N/10 c.c.	Ammonia N/10 c.c.	Acid + Ammonia N/10 c.c.	Acid ÷ Ammonia	NaCl
25	540	900	1.022	43.5	5.1	485	716	1,201	0.68	3.0
26	640	2,180	1.012	57.5	5.7	262	430	692	0.61	17.0
27	990	3,420	1.011	83.0	7.3	34	265	299	0.13	24.2
28	870	5,940	1.009	117.0	7.4	0	118	118	0.00	38.2
Mar. 1	1,000	4,120	1.010	90.2	7.3	41	108	149	0.38	28.4
2	1,300	2,200	1.013	63.0	7.2	66	85	151	0.78	16.0
3	985	1,580	1.020	70.0	7.0	126	85	211	1.58	9.9
4	1,455	1,700	1.016	60.0	5.9	235	143	378	1.64	9.6
5	1,500	600	1.030	26.4	5.1	252	164	416	1.54	2.4
6	1,190	1,120	1.020	51.7	5.3	415	276	691	1.50	4.5
7	1,450	840	1.024	44.4	5.3	336	300	636	1.12	2.5
8	1,500	800	1.030	35.2	5.2	326	300	626	1.09	2.2
9	1,500	1,030	1.019	42.6	5.1	344	364	708	0.95	3.8
10	1,500	900	1.019	37.6	5.0	336	356	692	0.95	4.0
11	1,300	1,050	1.018	†	...	...	...	...	....	...
12	1,680	780	1.025	42.0	5.3	300	300	600	1.00	5.9
13	1,700	720	1.024	38.0	5.3	238	288	526	0.83	8.2
14	1,500	880	1.023	44.5	5.3	300	306	606	0.98	11.8
15	1,500	1,020	1.020	44.9	5.3	420	400	820	1.05	8.2
16	1,500	880	1.017	33.0	5.3	264	238	502	1.11	6.2
17	1,500	‡	.....	....	...	...	...	...	....	...

* Hydrogen ion concentration expressed as the logarithm of the actual value. The minus sign is

‡ Two grams of lactose excreted in eight hours. Seven and one-half grains potassium iodid excreted in

—IN CASE 2 ON SALT-LOW DIET

NaCl per cent	Food Nitrogen	Total Nitrogen in Urine	Nitrogen Balance	Food, Calories	Weight, Pounds	Diet
0.33	4.8	.....	.....	.....	.....	500 c.c. milk.
0.78	7.4	7.80	— 0.4	987	.....	640 c.c. milk.
0.71	8.3	8.80	— 0.5	1,118	161½	800 c.c. milk.
0.64	5.9	8.75	— 1.8	1,028	149½	800 c.c. milk.
0.68	8.5	7.90	+ 0.6	1,141	136½	1,000 c.c. milk, 60 gm. salt-free bread, 1 boiled egg, 30 gm. butter.
0.73	9.8	7.95	+ 1.9	1,316	128½	1,000 c.c. milk, 60 gm. salt-free bread, 1 boiled egg, 30 gm. butter.
0.63	8.3	8.30	0.0	1,129	123	1,000 c.c. milk, 60 gm. salt-free bread, 1 boiled egg, 30 gm. butter, 200 c.c. milk added.
0.57	12.1	.....	.....	2,192	120¾	1,000 c.c. milk, 60 gm. salt-free bread, 1 boiled egg, 30 gm. butter, 200 c.c. milk added.
0.40	12.1	.....	.....	2,192	119	1,000 c.c. milk, 60 gm. salt-free bread, 1 boiled egg, 30 gm. butter, 200 c.c. milk added. Add to diet following: 40 gm. bread, 30 gm. butter, 1 orange, 300 c.c. milk.
0.40	10.5	.....	.....	1,994	118	1,000 c.c. milk, 60 gm. salt-free bread, 1 boiled egg, 30 gm. butter, 200 c.c. milk added. Add to diet following: 40 gm. bread, 30 gm. butter, 1 orange, 300 c.c. milk.
0.30	14.0	.....	.....	2,569	117	1,000 c.c. milk, 60 gm. salt-free bread, 1 boiled egg, 30 gm. butter, 200 c.c. milk added. Add to diet following: 40 gm. bread, 30 gm. butter, 1 orange, 300 c.c. milk.
0.28	14.0	.....	.....	2,569	117½	1,000 c.c. milk, 60 gm. salt-free bread, 1 boiled egg, 30 gm. butter, 200 c.c. milk added. Add to diet following: 40 gm. bread, 30 gm. butter, 1 orange, 300 c.c. milk.
0.57	14.0	.....	.....	2,569	117¾	1,000 c.c. milk, 60 gm. salt-free bread, 1 boiled egg, 30 gm. butter, 200 c.c. milk added. Add to diet following: 40 gm. bread, 30 gm. butter, 1 orange, 300 c.c. milk.
0.44	14.0	.....	.....	2,569	117	1,000 c.c. milk, 60 gm. salt-free bread, 1 boiled egg, 30 gm. butter, 200 c.c. milk added. Add to diet following: 40 gm. bread, 30 gm. butter, 1 orange, 300 c.c. milk.
.....	14.0	.....	.....	2,569	117	1,000 c.c. milk, 60 gm. salt-free bread, 1 boiled egg, 30 gm. butter, 200 c.c. milk added. Add to diet following: 40 gm. bread, 30 gm. butter, 1 orange, 300 c.c. milk.
0.76	14.7	.....	.....	2,704	116½	1,000 c.c. milk, 60 gm. salt-free bread, 1 boiled egg, 30 gm. butter, 200 c.c. milk added. Add to diet following: 40 gm. bread, 30 gm. butter, 1 orange, 300 c.c. milk. Add 50 gm. bread, 10 gm. NaCl.
1.14	14.7	.....	.....	2,704	118	1,000 c.c. milk, 60 gm. salt-free bread, 1 boiled egg, 30 gm. butter, 200 c.c. milk added. Add to diet following: 40 gm. bread, 30 gm. butter, 1 orange, 300 c.c. milk. Add 50 gm. bread, 10 gm. NaCl.
1.34	14.7	.....	.....	2,704	118¼	1,000 c.c. milk, 60 gm. salt-free bread, 1 boiled egg, 30 gm. butter, 200 c.c. milk added. Add to diet following: 40 gm. bread, 30 gm. butter, 1 orange, 300 c.c. milk. Add 50 gm. bread, 10 gm. NaCl.
1.80	14.7	.....	.....	2,704	118	1,000 c.c. milk, 60 gm. salt-free bread, 1 boiled egg, 30 gm. butter, 200 c.c. milk added. Add to diet following: 40 gm. bread, 30 gm. butter, 1 orange, 300 c.c. milk. Add 50 gm. bread.
0.68	14.7	.....	.....	2,704	118	1,000 c.c. milk, 60 gm. salt-free bread, 1 boiled egg, 30 gm. butter, 200 c.c. milk added. Add to diet following: 40 gm. bread, 30 gm. butter, 1 orange, 300 c.c. milk. Add 50 gm. bread.
.....	.....	.....	.....	.....	.....	

omitted. † Phenolsulphonephthalein 90 % in two hours.
forty-eight hours. Non-coagulable nitrogen in the blood—40 mg. to 100 c.c. blood. (Kindness of Dr. Denis.)

tian,[10] Georgopulos[11] and Widal.[12] The connection between sodium chlorid and edema is well established.

The chief point of contention centers about the question whether the retention of salt is the cause or the result of water retention. Many authors, Strauss,[8] Widal,[7] Halpern,[13] Castaigne[14] and others, believe that salt retention in the tissues is primary. If saline solution be injected into normal animals and animals in which nephritis has been produced experimentally, no difference is to be found in the urine, whereas, if both animals are bled and saline solution injected soon after, the blood of the nephritic contains less salt. These experiments led Castaigne to favor the primary salt retention theory. Salt retention in certain febrile diseases as lobar pneumonia, typhoid fever, rheumatic fever, gastric carcinoma and tuberculosis is considered by Achard,[15] Loeper,[15] Laubry[16] and Müller[17] as further evidence of primary salt retention. Georgopulos[11] believes the kidney becomes impermeable to water so that sodium chlorid is retained to satisfy the laws governing osmotic pressure in the body. The impermeability on the part of the kidney to salt is deemed of prime importance by Widal, Strauss, Halpern, Schlayer and others. Evidence was early presented by Cohnheim and Lichtheim[18] that injury to the capillary walls leading to increased permeability to salt probably played an important part in salt retention. They were not able to produce edema of the subcutaneous tissues by injecting large amounts of saline solution until the tissues had been injured in some way. Magnus[19] confirms this view in experiments, in which he was not able to produce a general edema by injecting large amounts of salt solution until he had poisoned the

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12. Widal, F.: Die Kochsalzentziehungskur in der Brightschen Krankheit, Verhandl. d. Cong. f. inn. Med., 1909, p. 43.

13. Halpern, M.: Beiträge zur Frage des Verhaltung der Chlorid im Körper, ihre Beziehung zur Oedembildung und ihre Bedeutung fur die Dietetik bei Nephritis, Beitr. z. wissensch. Med. u. Chem. (Festschr. f. Salkowski), Berlin, 1905, p. 125.

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15. Achard and Loeper: Sur la rétention des chlorures dans les tissues an coeurs de certains états morbides, Compt. rend. Soc. de biol., 1901, p. 346.

16. Achard and Laubry: Injections salines et rétention des chlorures, Semaine méd., 1902, xxii, 105.

17. Müller, F.: Morbus Brightii, Verhandl. d. deutsch. path. Gesellsch., 1905, ix, 64.

18. Cohnheim, J., and Lichtheim, L.: Ueber Hydrämie und hydrämisches Oedem, Virchows Arch. f. path. Anat., 1877, lxix, 106.

19. Magnus, R.: Ueber die Entstehung der Hautoedem bei experimentelle hydrämischer Plethora, Arch. f. exper. Path. u. Pharm., 1899, xlii, 250.

animal with either arsenic, chloroform, chloral hydrate or ether. Müller believes there is some toxic agent which renders the capillaries more permeable to chlorids. His view is shared by Jackson and Elting.[20] After reviewing the many cases reported in the literature, one is impressed with the fact that any one explanation is frequently inadequate for all the various conditions encountered. In most of the cases reported there is definite kidney disease or marked circulatory disturbance. Persistent hereditary edema of the lower legs (Milroy's disease), general edema occurring in children with gastro-intestinal disturbances, angioneurotic edema and edema neonatorum need not concern us here.

Jackson and Elting[20] have reported a case of edema in which there was no evidence of kidney disease, but the patient had been working for years in a vitiated atmosphere due to the decomposition of linseed oil, gums, resins and hydrocarbon compounds. The history was one of gradually increasing edema until it became very marked. Examination of the heart, lungs and urine were negative. The treatment with a salt-low diet, sweating and the usual diuretics had no effect on the edema. A marked diuresis with a large increase in the sodium chlorid elimination followed the administration of potassium nitrate. As Jackson and Elting were able to find no anatomical condition to explain the edema in their case they concluded that increased permeability of the capillaries to salt due to certain toxins and the increased combining power of the tissues for chlorids could best account for the condition.

In the cases here reported there is no evidence of kidney disease as determined by the usual urinary examination. The chief points of interest in the first case are, a history of a kidney of pregnancy, recurrent attacks of generalized edema usually associated with constipation, relief from symptoms on a salt-low diet and freedom from constipation, and a marked decrease in chlorid excretion in the urine after the addition of the small amount of 6 grams of salt to the intake. There seems to be definite incompetency on the part of the kidney to excrete chlorids. Although the kidney is able to take care of 2 to 3 grams daily, any increase in the demand for sodium chlorid excretion temporarily, at least, markedly reduces this particular function. That the bowel is important in the excretion of salt in this case seems very probable. The rôle of the bowel in chlorid elimination has been studied by Javal[21]

20. Jackson, H. C., and Elting, A. W.: Clinical Notes and Physicochemical Study of Salt Elimination in the Urine of an Individual with General Edema of Obscure Origin, Followed by Cure, Albany Med. Ann., 1909, xxx, 74.

21. Javal, M. A.: De l'elimination du chlorure de sodium par la diarrhée, Semaine méd., 1903, xxiii, 224.

and Halpern,[13] who found that normally and usually in nephritis the salt excretion by bowel is insignificant, amounting to a few tenths of a gram daily; in nephritis, however, with or without diarrhea, there may be as much as 3 to 5 grams excreted in the feces daily.

The data presented in connection with the second case are interesting. Following a day's rest on a restricted diet there occurred a quite remarkable urinary crisis. During five days, February 26 to March 2, inclusive, on a total fluid intake of only 4.7 liters the urinary output was nearly 18 liters. The loss in weight was 41½ pounds, or nearly one-third of the normal weight.[22] The total chlorid ingestion was not more than 15 gm., while the excretion was 124 gm., or 109 gm. in excess of the intake. On February 28 the sodium chlorid excreted was over 38 gm., or 35 gm. in excess of the day's ingestion, a record which I have not seen equaled in the literature. Cases with marked urinary crises are reported. In 1905 Rolleston and Attlee[23] reported a case of a man aged 36 with nephritis who lost 64½ pounds in sixteen days while taking caffein citrate, gr. 7, three times a day. Rolleston and Goda,[24] in 1909, reported a case of nephritis in a man of 27 who lost 59 pounds in four days, the only therapy being hot air baths.

Relative to the salt metabolism in the second case the effect of the addition of salt to the diet on February 12, 13 and 14, is interesting. During these three days 30 gm. of salt with the salt in the diet, which may be estimated as 9 gm., making a total of 39 gm., were ingested. For the three days the total excretion is only 26 gm., nor is the difference to be found in the day following. It should also be noted that there was no gain in weight. That there can be chlorid retention without edema has been shown by Ambard and Beaujard.[25] But it seems improbable in this case. With the history of the preceding case in mind, it is interesting that during the three days of extra salt he had three to four loose dejections daily. Unfortunately, the importance of this was noticed too late to save the feces for chlorid estimations. The percentage of sodium chlorid in the urine indicates, according to Schlayer and his school, little trouble with the function of the tubules of the kidney. Through the diuresis the percentage was constant, diminishing considerably after the disappearance of the edema to a minimum of 0.28 per cent., and increasing as markedly on the addition

22. Unfortunately the patient was not weighed until he had been in the hospital two days. From his urinary output it is safe to say that his loss in weight was nearer 50 pounds than 40.

23. Rolleston, H. D., and Attlee, John: Extraordinarily Rapid Diminution of Renal Dropsy under Citrate of Caffeine, Lancet, London, 1905, ii, 1394.

24. Rolleston, H. D., and Goda, F. L.: A Case of Edema with Resolution by Urinary Crisis, Brit. Med. Jour., 1909, i, 330.

25. Ambard, L., and Beaujard, E.: La rétention chlorurée sèche, Semaine méd., 1905, xxv, 133.

of salt to a maximum of 1.34 per cent. without any increase in the urinary output.

The behavior of the acid factors are very suggestive. From a highly acid urine, 5.1, on the day of entrance it rapidly became alkaline, 7.4 (approximately the reaction of normal blood). Contrary to what might be expected, the titratable acid and ammonia were much reduced on the day of the largest amount of urine. On the first day the total acid excretion on a low diet was 1,201 c.c. as against the normal 687 c.c. on a full diet for a hydrogen ion concentration only slightly lower.[26] During the first few days the ratio of acid to ammonia was normal, but following the diuresis there was an increase in the acid over the ammonia, a relation which I have found to be significant in certain types of nephritis.[27] This low ammonia, however, persists for a few days only. Its significance in this particular case is uncertain. It has been shown that mild grades of acidosis undoubtedly exist in many cases with edema.[28] The significance of the peculiar acid factors in this case is not clear, but some disturbance in body reaction seems probable.

Rather more phenolsulphonephthalein, 90 per cent., was excreted in two hours than is normally the case. Baetjer,[29] and Pepper and Austin[30] have reported several cases of nephritis in which the phenolsulphonephthalein excretion was higher than normal. Baetjer also found increased permeability to lactose with a normal potassium iodid output, a condition which he calls superpermeability of the kidney. In my case the lactose was somewhat delayed if the normal excretion of 2 grams of the substance intravenously be considered as six hours. The time of the potassium iodid output was within normal limits, forty-eight hours. In Baetjer's cases, as also in mine, the non-coagulable nitrogen in the blood was not abnormally high.

In the second case the following facts seem to me important: First, extensive generalized subcutaneous edema in the absence of any discoverable renal disease or irritation; second, mild circulatory symptoms but a distinct cardiac enlargement and a well-marked arteriosclerosis; third, a rapid disappearance of the edema on rest and diet. This evidence throws a strong suspicion on the circulatory system as playing a prominent part in causing the attacks of edema. The response of

26. Henderson, L. J., and Palmer, W. W.: The Several Factors of Acid Excretion, Jour. Biol. Chem., 1914, xvii, 305.

27. Unpublished data.

28. Palmer, W. W., and Henderson, L. J.: Chemical Studies on Acid Base Equilibrium and the Nature of Acidosis, THE ARCHIVES INT. MED., 1913, xii, 153.

29. Baetjer, W. A.: Superpermeability in Nephritis, THE ARCHIVES INT. MED., 1913, xi, 593.

30. Pepper, O. H. P., and Austin, J. H.: Interesting Results with the Phenolsulphonephthalein Test, Am. Jour. Med. Sc., 1913, cxlv, 254.

the body to additional salt by only a moderate increase of salt in the urine, although there was a nearly normal increase in the percentage, and the associated diarrhea, suggest some renal impermeability to salt.

SUMMARY

The cases reported illustrate again the well-known relation between sodium chlorid and edema, and suggest a possible explanation in some cases of edema of obscure cause. The impermeability to salt on the part of the kidney is an important factor.

Attention is called to the bowel as a vehicle for the excretion of salt. This fact is important in the treatment of cases with edema of obscure origin.

In certain types of edema there may exist mild grades of acidosis which may play some rôle in the persistence of the condition.

BOOK REVIEWS

L'Alternance du Coeur: Etude Critique et Clinique. Par Laurent Gravier; Moniteur d'Histologie à la Faculté de Médecine de Lyon. Paris: J. N. Bailliere et Fils, 1914, pp. 429.

When it is possible to publish a book of 429 pages devoted to the single symptoms of alternation, the study of the arhythmias of the heart may be said to have reached a point of great intensity. In undertaking his task Gravier has brought together all that is known of fact and of theory on the subject. He recalls that it was Traube, so many of whose suggestions regarding the clinical pathology of the heart have borne valuable fruit, who in 1872 first devised the term and described the condition. The present insight into the subject of alternation, however, dates really from about 1900, when the studies of Mackenzie and Wenckebach began to enrich this field. The definition of the rhythm which Gravier adopts and from which there can be no substantial difference of opinion is that it represents a variation (an alternation) in the force of succeeding contractions without an alteration in their rhythm; equidistance in time is maintained among succeeding beats.

Gravier describes alternation depending on ventricular contraction, as manifested in cardiograms, in arteriograms, in phlebograms and in electrocardiograms; alternation of auricular contractions is described from the same points of view. The theories which have been advanced to explain the occurrence of alternation are stated and minutely discussed. In the last section, the etiology, prognosis, and therapy are described.

The relation of alternation of the heart to the electrocardiogram has a special interest. Alternation in the height of *R*- and *T*- waves have been described by numerous observers, but the question whether electrical alternation has the same significance as alternation in mechanical curves of arteriogram or cardiogram, and whether the two run parallel, is still much discussed. Gravier, in reviewing the field, concludes that electrical alternation is often wanting when mechanical alternation is marked, and when present may be less marked than the mechanical. On the other hand, the electrical variety may exist without the mechanical, and in still other cases, when both appear, small mechanical waves correspond to tall electrical waves, and vice versa. But the important point seems to be that alternation depends for whatever prognostic value can be assigned to it, on the mechanical curve. So far as curves showing the electrical variety do not supply information of this order, mechanical ones must be made to provide it.

Two main theories of alternation have been advanced, that of Wenckebach, who describes it as the occurrence of hyposystole affecting the ventricles as a whole; and that held among others by Hering and proposed by Gaskell, who believe it to depend on asystole of a portion of the ventricular wall. For its production the Wenckebach theory depends on the varying durations of systole and diastole, a long diastole being followed by a stronger contraction. The Gaskell-Hering theory, according to which it is believed that a portion of the ventricular muscle fails altogether to contract, depends on the idea that this portion continues in a refractory period when the rest of the ventricle is ready to beat, and a weak beat results. At the next contraction, all the muscle is again fit, and a strong beat is made. Gravier's discussion of these theories is detailed and careful. It suffices to say that after weighing the evidence, he inclines to accept the partial asystole theory of Gaskell. As to whether the occurrence depends on one of the special functions, irritability, conductivity, or contractility, authors are divided, but most agree to its being associated with a defect in the last. Gravier prefers not to commit himself on this point, and thinks it sufficient to call it a "disorder of the refractory phase."

The causes of the irregularity are found to lie in infections and cachexias and in the heart failure of the various cardiovascular diseases. As to the significance of its presence, one may say that in severe states of disease its presence is not necessarily of evil omen, but indicates a situation the interpretation of which demands caution. On the other hand, alternation may be absent, even in terminal conditions.

This study of Gravier's deserves commendation on the grounds of thoroughness, completeness, and thoughtfulness. It is written with the clearness and simplicity characteristic of French writing.

THE LIFE AND LETTERS OF NATHAN SMITH, M.B., M.D. By Emily A. Smith. With an Introduction by William H. Welch, M.D., LL.D., Price, $2.25. New Haven: University Press, 1914.

This brief, clear and intimate study of one of the master minds of American medicine is most timely. Our medical biography is meager; Nathan Smith is one of its most attractive subjects. We are rapidly obliterating some of his creations and our methods have been so changed that his struggles will become increasingly difficult for us to understand. The work is brief, like Smith's own masterpiece, his work on typhoid fever. Documentary material was scanty, but fortunately it was telling, and the author had used it with conspicuous skill. There is in the first place the picture of the man, a heroic figure, like his younger contemporary Beaumont. His courage and resourcefulness, that were so often tried later, showed as a lad when, a militia soldier fighting Indians, he was made a captain at the age of 18. His relation to medical education, as student and teacher, illustrates some aspect of medical schools not only forgotten, but misunderstood. When he wished to study medicine there were only three schools in the young and sparsely settled country, practically devoid of means of communication. The so-called colleges and universities neglected professional education as they did for a century afterward. We can see the enthusiastic youth working hard to acquire a sufficient preliminary education to satisfy the man he had chosen as his preceptor. We have to imagine the toilsome three years of apprenticeship with the older man. Two years later the results of practice had lighted an unquenchable longing to learn from others more fortunate, and a year at Harvard medical school, then at Cambridge, followed. Then came the burning desire to found a medical school, not for a title, not for money, but in order to enable others to gain a knowledge of medicine under better conditions than he himself had had. The early struggles and disappointments at Dartmouth were probably not extraordinary, but there is something profoundly touching in the year of exile, away from his young wife, in Edinburgh and London. The beginning of the Dartmouth school and the labors there as a whole faculty, as well as physician, surgeon, obstetrician and specialist to the district, have been told by brilliant writers, but here one can learn from brief letters, as from the scanty strokes of a master etcher. We see also, besides the full and successful life, the misunderstandings, obstacles and regrets. How successful, appears from the fact that in a given period Dartmouth graduated nearly 50 per cent. more physicians than did Harvard. Then came the call to Yale, with honors, appreciation, larger opportunities, and the same strenuous life. Later came work at Bowdoin, where he began the summer course, and at Vermont. The careers of the sons, one of whom became as famous as the father, are briefly set forth. The work makes it clear that the memorials of Nathan Smith should be treasured as those of Sydenham. His virtues may be emulated even in these days of specialization. His "keen discriminating inquisitiveness," his unconquerable spirit in the face of difficulties — which indeed he overcame without thinking about that feature, will always be necessary in the study and practice of medicine. The preface by Dr. Welch illuminates the period and the work itself. The typographic and other mechanical features are attractive, and the little book should have many readers.